CLINICAL ENDOCRINOLOGY. I

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Preface

CLINICAL ENDOCRINOLOGY is a broad field of science and medicine with no very well defined borders. To the internist, it is a subspecialty; to the investigator in one of the natural sciences, it is a stimulus to research. Granting that a precise definition of endocrinology is not easily made, there is a general idea of its scope, but what is clinical endocrinology? "Clinical" means that the subject has to do with sick people, and the study of diseases and the treatment of the sick is the province of the physician. However, clinical endocrinology is not confined by the walls of hospitals, and it owes its rapid development to the contributions from many other kinds of endeavor.

In this book, sharp lines have not been drawn between what is clinical and what might be considered nonclinical However, the emphasis is mainly on clinical matters and on lines of inquiry which seek to reach a fuller understanding of normal and abnormal endocrine processes in human beings

The aim has been to provide concise authoritative articles written by specialists in the light of personal experience in their respective subjects. In a few instances, when it seemed desirable, more extensive reviews have been presented Some of the latter have included fairly complete documentation, but in most cases only key references to source publications have been cited. Complete coverage of the entire field has not, of course, been attempted in a single volume. Classic and well established material has been omitted to make way for topics selected largely on the basis of their current interest and importance. As a consequence, some areas have been dealt with more thoroughly than others and some subjects have not received the attention that they would have deserved in a work of more extensive scope. Within the framework of these limitations, however, a great deal of useful information and many interesting articles on a fairly wide range of topics have been included, giving, at the least, a broad view of the subject as a whole

By selecting the subjects, and especially the contributors, with great care, it has been possible to avoid contradiction, if not controversy, without introducing excessive dogmatism. Uniformity of style, an ideal achieved only by having a single experienced author, has not been achieved, but some effort has been made to attain simplicity of expression

The title chosen for the book needs explanation. Ten years ago, *Progress in Clinical Endocrinology* was published by Grune & Stratton under the editorship of Dr. Samuel Soskin It proved to be an interesting and most useful volume. Endocrinologists found it a practical source of reference, it

was recommended to medical students and general physicians used it as an introduction to specific topics of interest to them. The best indication of its success is the fact that a strong, continuing demand has existed for the volume even after exhaustion of a very substantial first edition. It seemed desirable, therefore, to publish a second edition, and it was to this end that the current project was initially directed. As the book took shape it was realized that it could not properly be regarded as a revision, since nearly all of the chapters were made up of new material written by new authors. Moreover, it was apparent that many of the contributions would be of lasting value as they stood Finally, it was recognized that other aspects of the subject could profitably be dealt with and that new areas would soon unfold and call for inclusion. It was therefore decided to title the book *Clinical Endocrinology. I* in the expectation that someone would have the time and the courage to bring together subsequent volumes containing additional and new material. Should this not transpire, the "I" will at least serve as a distinctive mark of bibliopegic decoration.

Boston, January 1960 E. B Astwood

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Clinical Endocrinology. I

I
PITUITARY

1
Control of Anterior Pituitary Function by the Central Nervous System

By MONTE A. GREER, M.D.

OVER THE PAST FEW YEARS there has been a rapidly expanding renewal of interest in the interrelationship of the two great integrative networks of the body, the nervous system and the endocrine system. Although the early history of endocrinology is filled with polemics concerning the relative importance of the hypothalamus and pituitary to the function of other endocrine glands, this debate largely became dormant following the demonstration by Smith of the primary importance of the pituitary gland and the ensuing isolation of potent pituitary extracts and purified hormones. It became generally accepted that the hypophysis secreted hormones which stimulated target endocrine glands. The target gland hormones, in turn, inhibited the release from the pituitary of their respective trophic hormones. Control of the adenohypophysis was assumed to be almost entirely humoral and to take place without any necessary mediation of the nervous system, although it was recognized that certain phenomena (e.g., persistent estrus produced by constant illumination) required a neural link.

Hypophysial Portal System

Harris[1] and Green[2] deserve a large share of the credit for revitalizing the concern with neural mechanisms involved in regulating pituitary activity. They have emphasized the universal presence of an hypophysial portal system in vertebrates. This system originates within the median eminence of the hypothalamus as a primary plexus of capillaries which coalesce to form trunks running down the infundibular stalk to the pituitary. There, these larger portal vessels again divide into capillaries which are distributed throughout the adenohypophysis.

This rather peculiar vascular structure appears to be of great importance to the optimal functioning of the anterior pituitary. Studies from many

laboratories have demonstrated that sectioning the pituitary stalk, which interrupts the portal vessels, will greatly decrease the release of trophic hormones from the adenohypophysis, as indicated by atrophy of the target endocrine glands and a reduction in their secretory activity. If the portal vessels regenerate, there is a return of pituitary function. Similarly, transplanting the pituitary to a heterotopic location, such as the anterior ocular chamber or the kidney capsule, produces gross decreases and distortions of hypophysial function If, however, the transplantations are made close to the median eminence so that a portal system can be re-established, a complete return of adenohypophysial function occurs even if the pituitary had first been grafted for a period of time at a distant site such as the kidney capsule

Because of the paucity of demonstrable innervation to the pars anterior, it has been concluded that there is no significant nervous pathway through which the central nervous system can influence the adenohypophysis. The assumption is that hypothalamic neurosecretory cells produce certain "neurohumors" which enter the capillary loops of the median eminence and are transported through the portal system to the anterior pituitary in which they control the secretion of trophic hormones. Although this is an attractive hypothesis, no unequivocal proof of the existence of such neurohumors has yet been brought forward

The hypothalamus is a very small area So many different functions seem to be localized within such a small space that one wonders whether certain nuclear groups might be pluripotential. Since the various activities can be independently modified by ablation or stimulation, however, separate areas are probably responsible for each function

It is well established that secretion of the various hypophysial trophic hormones can proceed independently If one assumes that there are discrete areas in the hypothalamus which control individual adenohypophysial secretions, two alternatives are possible Either there are separate neurohumoral materials which activate secretion of individual adenohypophysial hormones, or there is a transport system capable of shunting a single or several substances to localized regions of the anterior pituitary which specialize in the production of a single hormone. Re-establishment of the portal system allows normal hypophysial function. Revascularization of the adenohypophysis after stalk section or grafting to the median eminence would certainly not be expected to permit the establishment of a specific shunting system, particularly when several pituitaries are transplanted Therefore, since no definite shunting mechanism of the hypophysial system seems to exist, it is unlikely that a single neurohumor can activate secretion of all trophic hormones.

This makes it somewhat improbable that the neurohypophysial prin-

ciples, particularly vasopressin, can mediate all the pituitary activations which have been claimed for them. If a substance introduced at the proximal end of the hypophysial portal system can reach all parts of the adenohypophysis equally, and if all trophic hormones can be secreted independently, a single substance can certainly not be expected to stimulate thyrotropin, corticotropin, somatotropin, etc.

There is also the question of whether the neurohumors can act only when they are present in high concentration at the pituitary cell sites after a short passage through the portal system or whether they can be effective after passing through the general circulation. There is some evidence to indicate that at least a part of the neurohumoral activity may be maintained after a trip through the body It is difficult to do more than speculate when there is no knowledge of how to assay neurohumors precisely, what they are or even if any exist

Extent of Central Nervous System Involvement in Pituitary Control

Many recent studies using destruction or stimulation of various areas of the brain have indicated that the hypothalamic region is the most important for the regulation of anterior pituitary function. The hypothalamic centers involved in the control of specific pituitary hormones appear discretely located. One can selectively depress the secretion of thyrotropin, gonadotropin or corticotropin by appropriate hypothalamic lesions without affecting the release of the other adenohypophysial products.

Destruction of various other nervous centers seems to modify only slightly the secretion of trophic pituitary hormones, although in some cases there does appear to be a definite change produced. The influence of extrahypothalamic areas is best established for the rhinencephalic-limbic system Stimulation or destruction of certain parts of the amygdala, in particular, have been found to alter gonadotropic and corticotropic secretions by the pituitary. It has also been reported that spinal section will prevent activation by certain types of stimuli which ordinarily result in increased corticotropin secretion

Servo Systems

It has long been known that an inverse relationship exists between the circulating levels of most target organ hormones and their respective pituitary tropic hormones A negative feedback mechanism seems to exist. For example, an increase in the level of thyroxine in the blood will result in a decrease in the output of thyrotropin by the pituitary

For many years, it had been assumed that this inhibitory effect was a direct one on the adenohypophysis itself. Some recent work had indeed

indicated that a systemically ineffective amount of target organ hormones would decrease the respective pituitary "tropin" secretion only when injected directly into the anterior pituitary Injection of the same amounts of hormone into various areas of the hypothalamus was ineffective

It has now been found in several laboratories, however, that transplantation of tiny bits of target glands or injection of small amounts of their hormones into various rather specific areas of the hypothalamus, as well as into the adenohypophysis, will selectively inhibit the secretion of the respective tropic hormones

These localized sites within the hypothalamus which are sensitive to altered concentrations of hormone seem to be specific "inhibitory" centers which actively depress individual pituitary secretions. Destruction of these inhibitory centers has been claimed to prevent the atrophy which usually results following administration of target organ hormone. Other circumscribed areas presumably are "stimulatory" and will cause increased hypophysial output of specific tropic hormones. If this concept is correct, there should be a basal, nonfluctuating secretion from an adenohypophysis isolated from neural influences There is considerable doubt that this is the case since at least some hypophysial secretions are inhibited by local administration of equally small doses of target organ hormone at both the hypothalamic and pituitary levels.

Thyrotropin

Transplantation of the pituitary to a heterotopic site reduces thyroidal activity. Similarly, a profound decrease in thyrotropin secretion can be produced by destruction of a mesial area of the hypothalamus stretching from the paraventricular nuclei to the median eminence [3] Electrical stimulation of this same area in rabbits will cause increased thyroidal secretion [4] Neither hypothalamic lesions nor pituitary relocation prevent increases or decreases in thyrotropin secretion in response to alterations in circulating thyroid hormone produced by administration of antithyroid drugs or thyroxine.

With both lesions and pituitary transplantation, the growth response of the thyroid to various stimuli is interfered with to a greater extent than is the metabolism of radioiodine by the gland It now appears fairly well established that the metabolic responses measured with radioiodine are sensitive to considerably smaller amounts of thyrotropin than is the growth response of the gland Lesions and pituitary transplantation thus probably merely reduce the total quantity of thyrotropin secreted.

Certain drugs which depress the activity of the brain, such as reserpine and morphine, have been reported to decrease thyroid function, but there is

no unanimity as to the results obtained and the data do not appear too convincing where positive results are claimed

Studies have been made of the localization of labelled thyroxine and triiodothyronine in the brain of different species.[5] It has been found that both concentrate to a certain extent in the paraventricular nucleus and around the median eminence, among other and probably nonspecific areas. The highest concentration seems to be in the posterior lobe of the pituitary, although there is also considerable localization in the anterior lobe in some species. Exactly what significance can be attached to the concentration of labelled thyroid hormones in various sites is uncertain at the present time. It seems probable there may be no connection between the concentration in some areas, such as the neurohypophysis, and the inhibition of thyrotropin secretion which thyroxine produces.

Microinjections of minute, systemically ineffective amounts of thyroxine have been made into localized areas of the hypothalamus and pituitary to see if a specific area is sensitive to increased local concentrations of thyroid hormones. Contrary to earlier results which had indicated that microinjections of thyroxine would inhibit thyrotropin secretion only if made directly into the anterior pituitary,[6] it has now been found that injections into the anterior hypothalamic "thyrotropin area" will also inhibit thyrotropin release.[7] The anterior hypothalamus and anterior pituitary seem to be equally sensitive to local alterations of thyroxine concentration, but the inhibition produced by injection into the pituitary is almost immediate whereas there is an 8 to 9 hour delay after injection into the anterior *hypothalamus*.

It is unlikely that the inhibition following intrahypothalamic injection is due to transport of thyroxine through the hypophysial portal system to the anterior pituitary, there to exert its effect. Only 1 per cent or less of labelled thyroxine injected into the anterior hypothalamus reaches the pituitary. Since the sensitivity of the two areas is approximately equal, the quantity of thyroxine which would thus reach the adenohypophysis following hypothalamic injection would be much less than the minimal amount required to produce inhibition of thyrotropin secretion with direct intrapituitary injection The significance of two separate centers which regulate the secretion of thyrotropin is not yet known.

Brown-Grant[8] has suggested that the hypothalamus may function in regulating thyrotropin secretion by acting as a "filter" to control the amount of thyroxine reaching the anterior pituitary. If this were true, it would be expected that the amount of thyroxine required to decrease thyrotropin secretion in animals with effective hypothalamic lesions would be less than that required in normal animals At least two laboratories have

found that this is not the case,[9, 10] although Purves[11] has reported that smaller amounts of thyroxine will inhibit thyrotropin secretion in the lesioned than in the normal rat.

The nature of the hypothalamic neurohumor (if such exists) which controls thyrotropin secretion is unknown at present. There have been various reports that saline or lipid extracts of the hypothalamus, vasopressin or oxytocin can stimulate secretion of thyrotropin. The data of these experiments are not convincing, and other investigators have not been able to confirm the original reports

Gonadotropin

Although the modulation of gonadal activity by the nervous system has been studied in greater detail and for a longer period than is the case with the other endocrine organs, only rudimentary comprehension of the interplay involved has yet been achieved. Various alterations have been found in the function and structure of both testes and ovaries following destruction of certain parts of the brain. Lesions involving the median eminence can result in severe gonadal atrophy closely simulating that seen following hypophysectomy. In the experience of some investigators, such severe atrophy is more readily produced in males than in females. Midline lesions between the paraventricular nucleus and median eminence usually cause persistent vaginal cornification and failure of ovulation and corpus luteum formation It has been assumed that this results from inadequate luteinizing hormone (L H) secretion. The persistent estrus will revert to regular cycles if small, daily doses of progesterone are administered, and in many cases the normal cycles will persist for several weeks after progesterone has been discontinued This indicates that the ability to secrete L H has not been permanently impaired

Similarly, rats kept under constant conditions have a "critical period" of two hours during which the mechanisms responsible for ovulation are set in motion Barbiturates, chlorpromazine and reserpine during this period will block ovulation [12] Electrical stimulation of the ventral hypothalamus from the optic chiasm to the median eminence will induce ovulation in these "blocked" animals,[13] again pointing up the importance of this area to cyclic ovarian activity.

Precocious puberty has been produced in some species by similar anterior hypothalamic lesions Recording technics have shown that there is activation of the a
ovulation in
estrous cats.
bundle.

Evidence has been presented by Flerkó that there is an anterior hypo-

thalamic "inhibitory center" important for the decrease in gonadotropin secretion produced by administration of gonadal steroids. Small ovarian fragments grafted in the region of the paraventricular nucleus will result in decreased uterine weight.[14] Similar ovarian grafts had no significant effect when placed in the adenohypophysis or mammillary region. Conversely, destruction of the paraventricular nucleus markedly lessened the inhibitory effect of systemic estrogen on gonadotropin production.

Other areas of the brain have also been explored for their importance to reproductive physiology. Stimulation of the medial amygdaloid nucleus will frequently result in ovulation. Amygdalectomy, depending on the species used and the procedure employed, can alter gonadal function in a variety of ways. In our experience with the rat, it seems to decrease gonadotropin secretion.

Because certain procedures which inhibit ovulation had been found to raise the threshold of the reticular activating system, it was believed that the mesencephalon might be an important pathway in the mechanism of ovulation. Critchlow has found that an area located rostrally to the meso-diencephalic junction, probably the rostral mammillary peduncle, will inhibit ovulation when destroyed.[15] Massive destruction of the midbrain tegmentum and resulting somnolence did not interfere with ovulation, indicating that neural mechanisms underlying behavioral arousal are not crucially involved in this process

Profound gonadal atrophy occurs when the pituitary is transplanted to a heterotopic location. Recently it has been found that although most hormone production is greatly reduced by relocation, secretion of luteotropin may actually be increased and maintained for a considerable period of time[16] (see Sec. VI, ch. 5).

The sex of the donor gland does not appear important. Male pituitaries will produce normal estrus cycles and pregnancy when grafted under the median eminence of females. The controlling factor in the type of gonadotropin produced by the adenohypophysis, therefore, must be dependent on the sexual differentiation of the central nervous system

The nature of the neurohumoral mediator of gonadotropin release is as uncertain as that theoretically controlling the other secretions of the anterior pituitary. Markee, Sawyer and Everett[17] have indicated that both an adrenergic and cholinergic component are sequentially involved in ovulation. However, there has been thus far no direct demonstration of any material which can be held responsible Electrical stimulation of the hypothalamus will result in ovulation, whereas direct stimulation of the adenohypophysis will not This suggests that there is no important neural link involved and lends further credence to the concept of a neurohumoral agent.

CORTICOTROPIN

Although there is some evidence that posterior hypothalamic lesions will prevent the acute release of corticotropin, most observers agree that the integrity of the anterior median eminence is essential for normal secretion of corticotropin Both indirect indices, such as adrenal ascorbic acid depletion and fall of circulating eosinophiles, and direct measurement of plasma and urinary adrenal corticoids have been used The general consensus is that lesions in the median eminence inhibit the release of adrenal steroids in response to stress whereas the adrenal gland does not atrophy and may even enlarge

The reverse picture is seen with pituitary transplants Although the adrenals are atrophic, there still is a response to acute stresses such as laparotomy or epinephrine injection when indirect parameters of adrenal function are employed As yet, no direct measurement of adrenal steroid output has been reported in animals with heterotopic pituitaries.

It has been proposed that the "metabolic" stresses, such as laparotomy, can still effectively activate corticotropin secretion in a pituitary gland isolated by transplantation or stalk-section whereas "neurogenic" stimuli, such as forced immobilization, are impotent However, the propriety of cataloguing these various stresses as neurogenic or metabolic is open to question.

The fact that in one type of preparation adrenal weight is maintained with a loss of corticosteroid secretion (or adrenal ascorbic acid depletion) while in another type the opposite is true suggests that there may be two separate corticotropins secreted by the pituitary. The adrenal weight factor and adrenal ascorbic acid factor are both theoretically under hypothalamic domination and each can be destroyed by appropriate hypothalamic lesions, but apparently only the latter can be activated once the hypophysis is removed to a heterotopic location Presumably, the hypothalamic neurohumor responsible for stimulating release of ascorbic acid factor is effective after passing through the general circulation whereas that responsible for the weight factor is not Although it may eventually be decided that a single corticotropin can produce these phenomena, a correct interpretation is difficult at this time

It is certainly true that there must be at least two types of corticotropin Quite some time ago it was found that hypophysectomy would cause a nonuniform atrophy of the adrenal cortex, sparing the zona glomerulosa [18] Sodium and potassium imbalance were not produced. Following the eventual discovery of aldosterone and the observation that secretion of this hormone is from the zona glomerulosa and not primarily dependent on the integrity of the pituitary, it was concluded that a nonhypophysial organ controls aldosterone secretion through a humoral mechanism. Studies with

various types of ablation[19] point toward the mesodiencephalic junction as the source of the aldosterone-controlling hormone, termed by Farrell "glomerulotropin." Currently, there is some evidence that glomerulotropin may be produced by the pineal, but no unequivocal proof of this is yet available (see Sec. V, ch. 6).

The nature of the hypothalamic "corticotropin releasing factor" (CRF) which stimulates glucocorticoid secretion is unknown. McCann has presented considerable evidence that this material may be vasopressin.[20] Diabetes insipidus is well correlated with inhibition of corticotropin release in animals with median eminence lesions. Vasopressin and corticotropin are simultaneously released by certain types of stimuli. Vasopressin in relatively large doses will cause corticotropin release in animals made unresponsive to stress by median eminence lesions. Similar doses are ineffective in hypophysectomized controls

However, there are many arguments against vasopressin being identical with CRF. Corticotropin and vasopressin are not always released simultaneously. Under certain conditions, one may be released and the other inhibited Fractionation of neurohypophysial extracts in some laboratories has shown that a material other than vasopressin has CRF activity Diabetes insipidus is not always correlated with decreased corticotropin release. Vasopressin has also been shown to cause increased corticoid secretion in hypophysectomized animals and to stimulate directly adrenocortical secretion when infused into the adrenal artery

Somatotropin

Although some interference with growth may be produced by hypothalamic lesions,[21] it appears that, in the rat at least, this is due to decreased secretion of hormones other than somatotropin. Replacement of appropriate target organ hormones will allow normal growth in the lesioned animals. Similarly, normal growth has been found in some species of animals with heterotopic pituitaries. However, clinical evidence suggests that lesions above the sella turcica may be associated with dwarfism

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2

Action of Growth Hormone in Man

By M. S. RABEN, M.D.

INFORMATION ABOUT THE PARTICIPATION of growth hormone in human physiology has been until recently limited to inferences from clinical and pathologic observations, particularly in dwarfism, gigantism and acromegaly. Disorders of the pituitary in young individuals may result in abnormalities in size of freakish proportions and in older individuals in disfiguring overgrowth of tissue. It was appreciated from observations of these aberrations that the pituitary was concerned with the regulation of growth. While it is known that without pituitary function dwarfism occurs, and that with excessive secretion of growth hormone from eosinophilic tumors gigantism occurs in the young and acromegaly in the mature, it is not known whether the quantity of growth hormone secreted determines the height of normal individuals nor whether the anabolic effects of growth hormone are important to the adult. Neither is it entirely clear which of the many metabolic effects observed with the administration of growth hormone preparations are of physiologic importance.

Since the over-all result of the action of growth hormone is an increase in nearly all the tissues and organs of the body, it might be anticipated that many indices of metabolic activity are altered in the course of this diffuse anabolic stimulus. The abundant evidence of changes in fat, carbohydrate, protein and mineral metabolism, as well as other aspects of the effects of growth hormone, has been summarized in several recent reviews.[1-4] The precise mode of action of growth hormone, however, remains undefined, and it is tempting to seek its primary effect in relation to the metabolic changes that are evident with the smallest doses of growth hormone. This can be a misleading approach since compensatory mechanisms may preserve constancy of the response or substance being studied. For example, small doses of appropriate pituitary preparations may precipitate diabetes in dogs or cats whose pancreatic function is restricted by partial removal or by damage from alloxan, while very large doses are required in the normal animal.

The mobilization of fat, as indicated by an increase in the fasting value of plasma unesterified fatty acid, appears from studies of both normal and hypopituitary individuals to be among the most sensitive measurements of the growth hormone effect and it is also a fairly rapid effect.[5] The importance of fat mobilization and utilization to the anabolic stimulus by

growth hormone has been a recurrent theme in animal experimentation for over 25 years, and the recent observations on fatty acids have permitted a closer inspection of the hormone's influence During the period between feedings when the tissues are largely dependent on fat depots for their energy requirements (see Sec VII, ch. 1), growth hormone in some manner augments the release of fatty acids by adipose tissue, but when sufficient carbohydrate is immediately available, as during the absorption of a meal, and there is insulin from either the pancreas or injection to permit effective metabolism of the carbohydrate, the outpouring of fatty acids ceases even with growth hormone present Growth hormone thus serves to insure an abundant supply of nonprotein calories to the tissues at all times, and perhaps this is an important part of the anabolic effect, provided that amino acids are also supplied from which proteins can be synthesized This line of thought is encouraged by the fact that while hypophysectomized rats fed ad libitum do not grow, hypophysectomized rats which are force-fed store nitrogen and grow in the absence of growth hormone, though only with amounts of food that lead to excessive deposition of fat The contrast of two anabolic hormones, growth hormone and insulin, is particularly striking in this regard. Administration of insulin to hypophysectomized rats induces excessive eating, and nitrogen retention and growth, but as in the force-fed animals, only with a disproportionate amount of fat formation Growth hormone tends to diminish fat stores and promotes lean tissue formation without the caloric wastage of fat deposition Growth hormone is ineffective in the total absence of insulin, but the metabolic distortions in this state would surely preclude anabolism The response to the growth-promoting activity of the hormone is also, for example, altered by the absence of thyroid hormone

While this discussion has emphasized the importance of fat mobilization in the response to growth hormone, there is no conclusive evidence to cite as to whether fat mobilization is a primary effect or secondary to another mechanism of anabolic action

Preparation of Growth Hormone for Human Use

There have been many attempts to obtain anabolic and growth-promoting effects in man with bovine and porcine growth hormone, but despite moments of transient optimism, preparations from slaughterhouse animals have not as yet proved useful in man. The idea of specificity of growth hormones received major support from the findings of Pickford and Wilhelmi[6] that fish growth hormone was inactive in rats and of Knobil, Wolf and Greep[7] that bovine and porcine growth hormones were inert in monkeys Although chemical differences dependent on the species of origin have been found with other peptide hormones (e g., insulin, vasopressin and corti-

cotropin) the variations are not sufficient to preclude activity in other species, in contrast with growth hormone. Recent immunologic studies have emphasized the specificity of growth hormones by showing that antibodies formed in the rabbit to human growth hormone do not react with porcine or bovine growth hormone but do cross react with simian hormone.[8-10]

Growth hormone prepared from human pituitaries produces its anticipated effects in man, and the preparation from simian pituitaries also appears to have biologic activity, although the usefulness of the latter material for prolonged treatment has not yet been tested. Human growth hormone may be purified from pituitaries removed at the time of autopsy and stored for months in acetone. Several methods of purification have been described, each yielding material with biologic activity in man.[11-13] The product of the glacial acetic acid extraction method was the first to be tested in man and to date has been the most extensively studied of the preparations.[12, 14, 15] Approximately 1 to 6 mg of growth hormone is obtained by this method from one adult pituitary It has been claimed that the concentration of growth hormone in human pituitaries is roughly the same at all ages, and therefore all pituitaries obtainable at autopsy are a potential source of human growth hormone.

Metabolic Effects of Human Growth Hormone in Man

Within four hours of the intramuscular administration of human growth hormone there is an increase of unesterified fatty acids in the plasma in fasting subjects,[5] and within 12 to 24 hours there is usually a fall in blood urea nitrogen[14] which has not been related to nutritional state. When the effect of growth hormone is observed in balance studies, as in the work of Beck,[15] Pearson,[16] Henneman,[17] Bergenstal,[18] Ikkos[19] and their associates, storage of nitrogen, phosphorus and potassium is usually seen The effects on calcium and sodium balance have been more erratic, but there is regularly an increase in urinary excretion of calcium, apparently independent of the calcium balance The storage of nitrogen is excessive for some days when growth hormone is administered daily, often as much as 3 or 4 Gm per day, but the amount retained then diminishes to quantities compatible with the requirements for growth It has been estimated that the nitrogen storage required for normal growth in children 9 to 13 years of age is about 0 3 Gm per day Nitrogen retention can be induced with growth hormone even when the diet is calorically inadequate, and the increased mobilization of fat from adipose tissue must be essential to the anabolic process in this circumstance The dose required for measurable nitrogen retention is of the order of 2 mg per day in a normal adult and 1 mg per day in a pituitary dwarf A single dose of as little as 0 5 mg caused a large increase

CHAPTER II · Methods of Study of the Patient

THE DISSEMINATION of knowledge regarding peripheral vascular diseases has lagged so far behind that of other fields of medicine that today many physicians feel insecure in determining the diagnosis of these diseases. It is important to realize that in the vast majority of cases the diagnosis can be made without the use of elaborate laboratory equipment or hospitalization Workers in this field have emphasized repeatedly that they are able to make most of their diagnoses from the history and careful examination of the patient That has been true in my experience also Elaborate studies serve primarily to clarify or substantiate the diagnosis or to determine quantitatively the relative degree of circulatory damage and residual or collateral circulation. It is therefore possible for any *practitioner of medicine to achieve proficiency in diagnosing the* condition of a patient who complains of circulatory disturbances For this purpose methods of history-taking and physical examination ordinarily taught by the medical schools and used in general hospitals are inadequate It is necessary to approach the patient's history from a somewhat different point of view, and the physical examination involves study of areas of the body not usually concentrated on during routine examination. In this chapter an attempt will be made to overcome these deficiencies

The establishment of the correct diagnosis is, of course, paramount to the determination of prognosis and proper therapy We shall assume that the physician has already conducted a routine, though detailed, inquiry into the history and examination

History from Point of View of Vascular Diseases

Certain points in the history should be re-investigated in detail. The patient should be encouraged to enlarge on his symptoms, since minute details of the story may give a lead to the ultimate diagnosis There are many facets to such an investigation

Perhaps the most frequent complaints are those of pain and discomfort in the legs These, of course, are vague descriptive terms and must be analyzed It is vital to know whether pain is present at all times or is present only at night and whether it is produced by exercise and relieved by rest The exact location must be determined One must discover whether the pain radiates down the back of the leg, as a sciatic type of pain, or whether it follows the course of the femoral vein, as is common in thrombophlebitis. It is important to know if it is limited to the joints of the feet and legs, as is common in diseases of the joints, or whether it is located in the calves of the legs, as is most frequent with vascular involvement; whether the pain is continuous and characteristic of venous thrombosis or of intermittent claudication produced by arterial occlusive disease such as arteriosclerosis obliterans With or without an ulcer or gangrene the pain may be localized in the tips of the toes, and this must be brought out in the history.

The same type of approach should be used when complaints concern the upper extremities. It is vital to know whether the pain is in the tips of the fingers, associated with ulceration or gangrene, or whether it is sharply localized under the nail, as is frequently the case with a glomus tumor. In other instances pain is described in the area of the axillary vein, as in cases of axillary thrombosis.

The physician should be prepared for complaints of vascular lesions involving many other areas of the body, for example, a to-and-fro murmur in the scalp, a thrill or bruit behind the clavicle or large varicose veins of the lower abdominal wall In each

CHAPTER II: Methods of Study of the Patient

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bophlebitis below the knees suggest early thromboangiitis obliterans. The history of chronic ulcers around or above the ankle with pigmentation and swelling of the leg suggests venous insufficiency of long standing.

The question of smoking has particular significance in patients with symptoms suggesting thromboangiitis obliterans and arteriosclerosis obliterans. If the patient has never smoked, thromboangiitis obliterans is, for practical purposes, ruled out as a possibility. The rare cases which have been reported in nonsmokers are considered by many workers to be of debatable authenticity The fact that the patient does not smoke does not affect the probability of arteriosclerosis obliterans, and this point may clarify the differential diagnosis of the two conditions.

The use of drugs is significant Ergot has been shown to have a definite effect on the vascular system which is described in detail in Chapter V. Many coal tar derivatives have caused increased capillary fragility with vascular hemorrhage Repeated injections of various types of serum and the use of sulfonamides have been suspected of having an etiologic role in periarteritis (polyarteritis) obliterans.

Sometimes the patient knows definitely that a sensation of numbness or lowering of temperature developed at a certain time. This frequently indicates a marked reduction of the blood supply to the involved extremity Contrariwise, a story of increase in temperature toward normal frequently indicates that the collateral circulation has been established

Detailed consideration of the foregoing points is presented in the discussion of the various diseases, but the importance of careful general inquiry cannot be overemphasized.

Physical Examination of the Vascular System

During the examination of a patient who is suspected of having or is known to have vascular disease, *it is essential that a complete*

instance it is imperative that inquiry be made regarding the entire vascular system. Too often the doctor concentrates on the most prominent lesion or area of discomfort, oblivious to the fact that the patient has a generalized vascular disease and that other aspects of this disease are far more important than the condition most prominently occupying the patient's attention. A large proportion of vascular diseases are generalized diseases. This must be kept constantly in mind in the study of each patient.

The mode of onset is important, as related to accident, surgery, frostbite, infectious disease or preceding malignancy. The exact history of trauma is of great importance, especially in the handling of compensation or industrial cases. Patients frequently relate the onset of their difficulties to the stubbing of a toe or the dropping of a tool on a foot. Careful inquiry, however, may reveal that the patient had difficulty in walking and pains at night on resting for weeks or even months before such an injury A thorough examination of the vascular system may reveal, in addition to an occlusion of an artery of the injured extremity, other evidence of advanced vascular disease The exact time relationship between an injury and the development of an ulcer of a toe should be determined The quality of pain, whether sharp and stinging or dull and aching, is worthy of careful inquiry

The patient will frequently provide a clue to the diagnosis if asked for details regarding color changes in the hands and feet. Blanching of the fingers on exposure to cold environment followed by erythema on return to a warm environment establishes a likely diagnosis of Raynaud's syndrome. The description of livid red hands with burning pain suggests erythermalgia (erythromelalgia). A description of red streaks extending up the leg should lead to speculation regarding the possibility of thrombophlebitis or lymphangitis.

The history of previous thrombophlebitis or thrombosis, with or without pulmonary embolism, often provides an important lead to the diagnosis. Repeated attacks in young males of throm-

RECORD FORM (Fig. 1)

Clinic No ... .

Date. ....

THE NEW YORK HOSPITAL

Vascular Clinic

Name: Sex: M S.W.D. Age:

Address: Race: Occupation:

Referred by: Birthplace

I. PRESENT COMPLAINTS (including duration, precipitating factors like temperature or injury; progression; previous therapy):

Enter appropriate descriptive word or phrase, do not use check mark.

Fatigue or claudication.
- location—
- severity—
- progression—
- produced by—
- relieved by—
- effect of heat or cold—

Rest pain:
- duration—
- location—
- severity—
- progression—
- relieved by—

Phlebitis:
- location—
- duration—
- recurrence—

Varicose veins:
- location—
- duration—
- previous therapy—

Lymphangitis:
- location—
- duration—

Color changes in extremities.
- at cardiac level—
- on elevation—
- on dependence—
- effect of cold—

Sensitivity to
- cold—
- heat—

Ulcers
- dates—
- general appearance—
- location—
- duration—
- previous healing—
- previous therapy—

Skin and subcutaneous changes (pigmentation, elasticity, trophic or fibrotic changes, coarseness, sweating):

survey of the vascular status be undertaken even though the pathology appears to be limited, such as gangrene of a single toe. It is equally essential that all observations be systematically recorded (Fig 1).

The patient should be completely undressed and should be examined in a room with good light Meticulous observation for unusual color changes or other abnormalities may give a clue to the primary condition, for example, the pulsations which may be seen in areas of the back associated with coarctation of the aorta The following case illustrates the need for this type of examination

A man, 44, worked as a bus driver in New York City. One Thanks giving Day there was a severe snow storm and he was exposed to considerable cold and dampness Two days later he noticed pain in the toes of his left foot, and soon gangrene developed in three of them He was admitted to a hospital where the diagnosis of arteriosclerosis obliterans and frostbite was made During 14 weeks in the hospital numerous attending physicians and members of the house staff saw him, concentrating their attention on the gangrene of the toes At the request of the Labor Commissioner of the State of New York I examined him

The patient was exposed completely. On observation alone it was apparent that the entire left leg and foot were lifted upward from the bed synchronously with each pulsation of the heart Without touching the patient I suggested that the resident place his hand under the popliteal space Great surprise was registered when a large popliteal aneurysm was palpated. The right leg also moved with rhythmic pulsa-

demonstrated that he did not have syphilis It was assumed, therefore, that the aneurysms had developed on the basis of congenital weakness of the walls or were mycotic aneurysms The gangrene was believed to be due to an embolic phenomenon from a thrombus in the popliteal aneurysm rather than to frostbite. Soft tissue x-ray studies for vascular changes showed no evidence of appreciable calcification of the arteries. An obliteration operation was recommended, but the patient refused surgery.

Approximately four months later the patient was again seen at an-

VIII GENERAL VASCULAR EXAMINATION.

ARTERY		Tortuosity	Vis. Puls.	Palp. Puls.	Tension on Puls	Nodulation
Temporal	R					
	L					
Brachial	R					
	L					
Radial	R					
	L					
Ulnar	R					
	L					
Femoral	R					
	L					
Popliteal	R					
	L					
Post-tibial	R					
	L					
Dorsalis ped	R					
	L					

FUNDUS R
L

VEINS (Describe)

IX OSCILLOMETRY

Maximum Readings	Right	Left
Foot		
Above ankle		
Below knee		
Above knee		
Hand *		
Above wrist		
Below wrist		
Above elbow		

X. OTHER TESTS—Allen test—enter P for patent, O for occluded

	Right	Left
Radial		
Ulnar		

XI SUMMARY AND CONCLUSIONS (Resume of history, physical findings, special tests and laboratory procedures. Indicate provisional diagnosis, further tests, emergency treatment and suggested course of therapy.)

*Record oscillometric readings taken at the wrist in adduction and with arm at 45°, 90° (abduction), 135° and 180° (hyperabduction) if readings are diminished in these positions Be sure to reduce oscillometric cuff pressure in each position to obtain maximal reading Record only maximal reading at each position

II. PERSONAL HISTORY.

Occupation, past and present
(possible industrial hazards):
Use of—
a. Tobacco (age of onset of use, kind and amount):
b. Alcohol (duration, kind and amount):
c. Others (arsenic, ergot, lead, etc.):
Exposure to unusual cold or dampness:
Exposure to chemicals:
Family history of vascular or other diseases:
Pediatric history:

III. *PAST HISTORY*

Diseases (vascular, cardiac, diabetes or other metabolic dysfunctions, infections, allergies, etc.):
Operations:
Frostbite or chilblains:
Pregnancies:
Venereal disease:
Variations in weight:

IV. GENERAL SYMPTOMATOLOGY:

V. GENERAL PHYSICAL EXAMINATION: Weight:
B.P.: R—
L—

VI. ORTHOPEDIC STATUS:

VII. EXAMINATION OF EXTREMITIES:
Skin changes (temperature on palpation):

Part	Effect of Elev.	Effect of Depend.	Color Changes Due to Cold	Trophic Changes	Gang.	Edema	Fungus
R arm hand							
L arm hand							
R leg foot							
L leg foot							

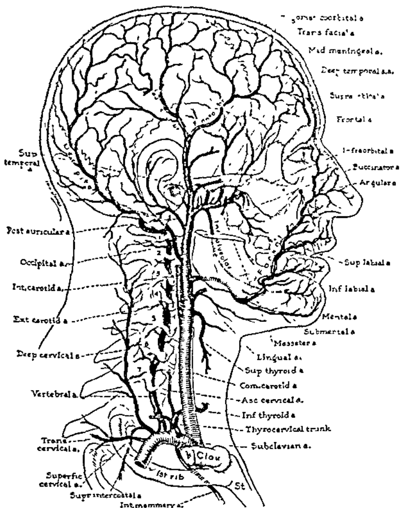


FIG. 2—Arteries of head and neck shown in relation to skeletal and body outline. (From Jones, T., and Shepard, W. C. *Manual of Surgical Anatomy* [1945]; reproduced by courtesy of W. B. Saunders Company)

other hospital, at which time an obligatory amputation was performed The aneurysm had become false, meaning that the sac had ruptured into the popliteal space Within the false sac was a large accumulation of clotted blood Careful pathologic examination failed to reveal the true cause of this aneurysmal defect.

Regardless of the site of the lesion or lesions of which the patient complains, the following procedure should always be adhered to in the examination (Figs. 2–4). The scalp should be palpated and auscultated for thrills or bruits, since arteriovenous anastomoses of the vessels of the scalp are not uncommon and intracranial anastomoses are encountered often enough to warrant this examination. Usually the patient is conscious of such a bruit, but this is not always the case, especially when the lesions are very small The temporal arteries should then be examined for tortuosity, plaques, tension, possible inflammatory reaction and thrombosis. In other words, the examiner seeks to determine whether these arteries are sclerotic and whether temporal arteritis is present The retinas should be examined for evidences of sclerosis, hemorrhage and exudate The possibility of central vein thrombosis must be considered if there is any visual disturbance.

The mouth and throat should be examined next. Note should be made of the degree of dilatation of the veins under the tongue; considerable distention while the patient is sitting up may indicate increased venous pressure The presumptive diagnosis of coarctation of the aorta, later proved, was once made by the shrewd observation by Dr. W. M. Ketcham that the arteries of the posterior wall of the pharynx were pulsating with unusual violence This is a sign that is rarely looked for. The vessels of the neck should then be palpated. Because of the complicated vascular structure in the upper areas of the neck, congenital arteriovenous anastomoses are not uncommon in that area. Bruits and thrills should be listened and palpated for. The carotid sinus area anterior to and high under the angles of the jaw bilaterally should be palpated cautiously and any unusual susceptibility, demonstrated by

marked slowing or actual stopping of the heart cycle, noted. Total absence of pulsation on palpation in the lateral aspects of the posterior pharyngeal wall may suggest internal carotid occlusion

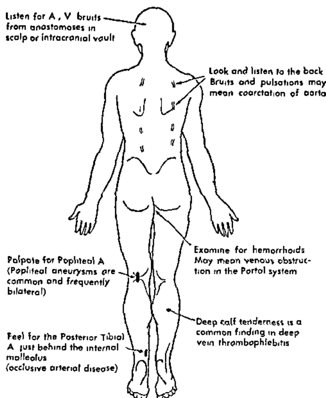


FIG. 4.—Posterior view, showing areas to be studied during examination for vascular diseases

Proceeding caudally, the examiner should focus his attention on the clavicular area, where aneurysms of the innominate and closely associated arteries are rather common, especially in elderly

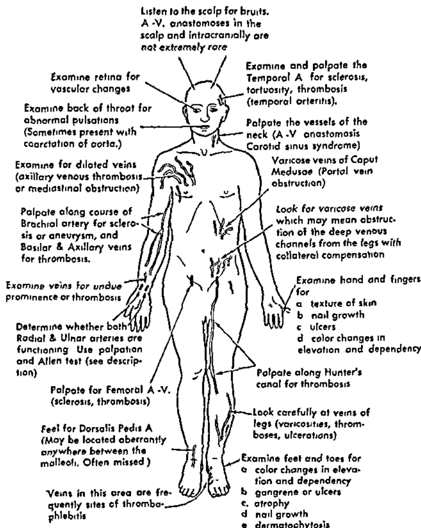


Fig 3—Anterior view, showing areas which should be studied during examination for vascular diseases, with mention of some, *but not all*, conditions which may be encountered This and Figure 4 should be carefully studied.

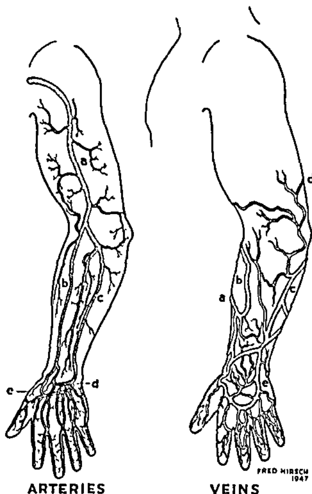


Fig. 5.—Semidiagrammatic projection of arterial and venous circulation of upper extremity. Arteries: *a*, brachial; *b*, radial; *c*, ulnar; *d*, superficial volar arch; *e*, deep volar arch. Veins: *a*, radial cutaneous; *b*, cephalic, *c*, anterior ulnar cutaneous; *d*, communicator to median; *e*, volar communication. (After Jones Quain, 1847.)

people The presence of such aneurysms is clearly indicated by an unusual degree of pulsation. Determination of the exact anatomic location of the vessel involved may be difficult without exploration because the arrangement of the vessels in this area differs somewhat in different individuals.

The pectoral area should be examined for dilatation of the veins. Venous dilatation will be found in the presence of axillary venous and superior vena cava thrombosis and in patients with lesions of the mediastinum which obstruct the venous return flow from the arms by extrinsic pressure. Passing caudally over the anterior surface of the trunk, the examiner should look for varicose veins of the upper area of the abdomen. The so-called caput medusa often indicates portal vein obstruction. Conspicuous varicosities in the suprapubic region and extending upward indicate obstruction of the deep venous channels returning from the leg, with collateral compensation These usually follow thrombophlebitis which has occluded the iliac veins or superior vena cava. Whenever varicose veins of the abdominal wall are found the direction of the flow of blood should be studied. Details regarding this will be found in the discussion of obstruction of the vena cava in Chapter XX.

Thorough examination of the upper extremities should now be undertaken (Fig. 5). Any degree of swelling or discoloration should be recorded. Note should be made of unusual dilatation of the veins, which may be due to thrombosis of the deep venous channels, obstruction to venous return flow in the mediastinum or the presence of arteriovenous anastomoses. Palpation should extend from the axillary area down to the elbow along the inner surface of the arm. The brachial artery should be palpated for pulsation, sclerosis or aneurysm, and the axillary brachial vein for evidence of thrombosis Proceeding to the area of the wrist, it is necessary to determine whether the radial and ulnar arteries are functioning Frequently the pulsations of both are easily palpated, but because in many individuals the pulsations of the ulnar

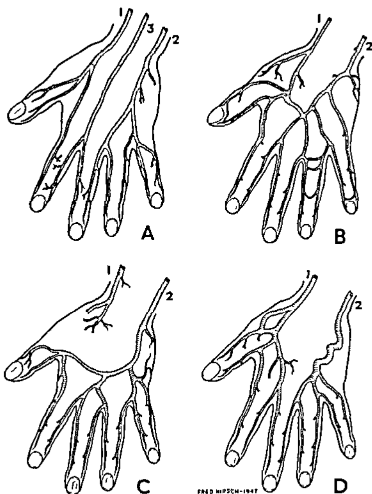


FIG 6—Semidiagrammatic projection of some principal variations in arterial supply of the hands *A–D*· *1*, radial artery, *2*, ulnar artery *A*, *3*, superficial interosseous branch of radial artery. (After Jones Quain, 1847.)

artery cannot be palpated, it is advisable to test for patency by the following modification of the method described by Allen

The examiner stands beside the patient and faces in the same direction With one thumb placed over the patient's radial artery and the other over the ulnar artery, the following maneuver is carried out The patient elevates his hand above his head and clenches his fist to force out as much blood as possible. The examiner presses his thumbs firmly to occlude the patient's radial and ulnar arteries The patient's hand is then lowered to a dependent position and it is opened, but relaxed, not stretched into hypoextension The hand remains pale. The thumb over the radial artery is then released Normally, a flush will spread rapidly over the hand and fingers from the radial side. If the radial artery is occluded, the hand will remain pale An identical test is then performed, but this time the thumb over the ulnar artery is released to determine whether or not it is patent Patches of residual pallor may indicate obstructive lesions in the arterial arch or smaller vessels of the hand or digits Both hands should be tested in this fashion

The Allen test is of especial value when a lesion of the ulnar artery is suspected and when the lesion of the radial or ulnar artery is peripheral to the point at which the thumb is applied

The hands should next be carefully examined for evidence of atrophy, change in color or texture of the skin and dermatophytosis. Inadequate nail growth or thickened nails should be noted. The nail beds should be examined for small slate-gray or blue spots which may be glomus tumors This is especially important if the patient complains of unexplained pain in the finger-tips. Pressure with a fine pointed object such as a pencil directly over the glomus tumor may elicit excruciating pain which may radiate up into the neck. This condition is frequently unrecognized, yet may easily be diagnosed by careful observation.

The upper extremities should next be placed in the position of hyperabduction with the patient seated or standing. Evidence of undue unilateral or bilateral pallor should be noted Pulsations of the radial and ulnar arteries should be tested in the position of hyperabduction to determine the presence or absence of the hyper-

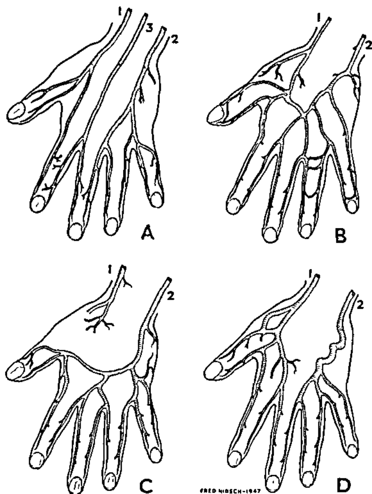


FIG. 6—Semidiagrammatic projection of some principal variations in arterial supply of the hands. *A–D* *1,* radial artery, *2,* ulnar artery *A, 3,* superficial interosseous branch of radial artery. (After Jones Quain, 1847.)

abduction syndrome (Wright). In this position the subclavian axillary artery may be pinched between the clavicle and the first rib, and it is also subjected to stretching and torsion under the coracoid process. This is described in detail elsewhere (pp. 285 ff.). The hands should then be placed in the dependent position and excessive rubor noted Changes in the pulsations with the arm extended and with the head turned away from or toward the side being examined should be noted. These may indicate the presence of a cervical rib or a scalenus anticus syndrome. The effect on the pulse of backward and downward displacement of the shoulders should be determined. If this maneuver causes blocking of the pulse it is probably due to the costoclavicular syndrome.

The patient's back should then be examined (Fig. 4). Although only exceptionally is first evidence of vascular disease found on the back, careful observation has in a number of instances revealed unusual pulsations indicating coarctation of the aorta or arteriovenous anastomoses and, in one instance, a large vascular tumor which had produced an arteriovenous anastomosis.

The anus should be carefully examined for external and internal hemorrhoids. The genitalia are next examined. The labia and vaginal walls may disclose marked varicosities following phlebitis with occlusion of the iliac and some of the pelvic veins. We have seen four women with such severe scleroderma that constriction of the vaginal opening prevented intercourse and a man in whom scleroderma prevented proper penile erection because of tightness of the foreskin Thrombophlebitis of the veins of the penis, although uncommon, is occasionally seen, usually following definite sexual trauma.

The lower extremities should next be studied (Fig. 7). Hunter's canal should be palpated carefully. It is important to note whether the pulsations of the femoral arteries are strong or difficult to feel. *Demonstration of thrombosis of the femoral vein by palpation of* the canal is often difficult because of enlargement of the inguinal and upper femoral lymph nodes, which may extend 3–4 cm.

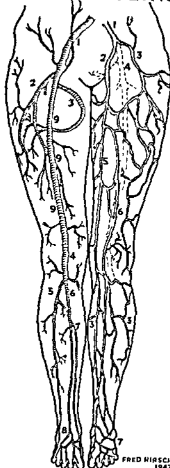


FIG 7—Semidiagrammatic projection of arterial and venous circulation of lower extremities Arteries *1*, common iliac; *2*, deep femoral; *3*, external circumflex; *4*, popliteal, *5*, peroneal, *6*, anterior tibial; *7*, posterior tibial, *8*, dorsalis pedis; *9*, femoral. Veins: *1*, common iliac, *2* and *5*, external saphenous, *3*, communicating veins, *4*, femoral, *6*, deep saphenous, *7*, dorsal pedal. (After Jones Quain, 1847)

along the femoral vessels. The upper thigh should be examined for varicose veins extending from the saphenous-femoral junction in all directions. Such varicosities usually indicate a former thrombophlebitis which destroyed the integrity of the saphenous valve. The femoral canal should then be palpated down along its course to the posterior surface of the knee. Evidence of thrombosis or arteriosclerosis should be noted.

The popliteal area should be very carefully examined. Sometimes it is difficult to determine the pulsation of the popliteal artery, but palpation should always be attempted. Frequently it is best done by having the patient lie in the supine position with the knees slightly flexed Another procedure is to have the patient lie prone with the knees slightly flexed while the examiner's fingers press in the popliteal space. This examination should never *be neglected because popliteal aneurysms are not rare, especially* in the older age group. The most common etiologic factor is arteriosclerosis, but they may occur in syphilis or follow trauma

The lower legs should be examined for varicosities of the superficial veins, edema and evidence of thrombosis and of ulcerations, which are rather frequent over the tibia and in the region of the ankle The posterior surface of each calf should be carefully but deeply palpated for evidence of deep venous thrombosis. Forced flexion of the foot (Homan's technic) may produce deep pain in the zone of the gastrocnemius muscle, suggesting the possibility of thrombophlebitis in that area. It is important that all ulcers be carefully described and measured for comparison. Tracing of the outline of the ulcer on a sheet of cellophane applied over it is the preferred method since it includes all the irregularities of contour. A series of such tracings will indicate whether or not the ulcer is decreasing in size during treatment. Clinical impressions are frequently fallacious in this regard The posterior tibial artery is then sought where it passes just posterior to the internal malleolus. It is important to determine whether this artery is pulsating or not.

The examiner then studies the patency of the dorsalis pedis ar-

tery which passes down over the anterior surface of the foot (Fig 8). It is most frequently felt somewhat to the medial side, 2–3 cm. distal to the level of the malleolus, but it should be realized that often this artery is aberrant and may be found anywhere between

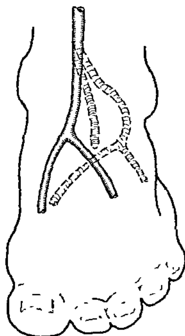


FIG. 8—Semidiagrammatic projection showing some variations in course of the dorsalis pedis artery These and other possible variations must be kept in mind when the vessel is not palpable at its usual site Left-hand outline, usual location of dorsalis pedis; center outline, artery curved laterally, right-hand outline, artery curved ventrally, lying deep between the bones, and pulse is not palpable

the anterior surfaces of the two malleoli Considerable time may be required to locate the artery even when it is pulsating freely. Patients have been referred several hundreds of miles because the physician failed to find the dorsalis pedis artery and concluded

that the patient had serious vascular disease. In numerous cases, careful palpation revealed that the vessel was aberrant, being located, for example, over the anterior surface of the external malleolus. The dorsalis pedis artery may be located deeply, so that it cannot be palpated, yet oscillometric readings will reveal its presence; this does not signify a circulatory disease. If the dorsalis pedis cannot be felt in either foot of a young man with *no other evidence* of vascular disease, the possibility that the condition is congenital must be considered.

One additional factor should be mentioned at this point. Spasm of the dorsalis pedis (1) in a cold examining room, (2) in the presence of extreme nervousness or (3) in a vasospastic patient may result in absence of pulsation without occlusive vascular disease. A heated examining room, reflex heat, obtained by the use of a heating pad on the abdomen, and reassurance or relaxation by mild sedation will in such instances restore the normal pulse, 1/100 gr nitroglycerin sublingually often brings out a strong pulse in arteries not organically occluded. Thus, absence of a readily palpable dorsalis pedis pulse may indicate: (1) an aberrant location of the artery at its usual depth; (2) a deeply placed artery; (3) spasm of the artery due to cold or nervousness, with or without a vasospastic diathesis, (4) organic occlusive vascular disease, or (5) pressure on a major artery above the level of examination. One of three cases in which a truss occluded the femoral artery follows.

A man, aged 77, complained of intermittent claudication in the right calf after walking a city block When first noted 12 years before, his physician had recorded absence of the right dorsalis pedis artery and oscillometric readings at 0 in the foot and 0.25 above the ankle He received more than 200 injections of various types without effect. In April, 1951, he was seen in the peripheral vascular clinic at the New York Hospital. At that time, 12 years after onset, no pulses could be palpated in the right foot. Oscillometric readings were 0 1 in the foot and 0 6 above the ankle. During a complete examination it was noted that he wore a truss with pads over both inguinal areas but with greater

pressure over the femoral artery on the right On removal of the truss, both pulses were easily palpated in the foot! Oscillometric readings increased immediately to 0 2 in the foot and 1 5 above the ankle. He was instructed to remove the pad on the right side of the truss, since it turned out that he had a hernia only on the left side and had added the pad on the right side on his own initiative 12 years before One week later he reported total absence of all claudication symptoms He had walked nearly a mile without pain.

The feet and toes should always be examined with great care because they are the areas most frequently involved in peripheral vascular diseases The examiner should study them for color changes on elevation and on dependency, for evidence of gangrene and ulcers, however small, for atrophy of the skin, muscles and nails and for evidence of impaired nail growth and dermatophytosis. It is important to examine the medial surface of the foot, *since the veins passing upward from the sole are common sites of* thrombophlebitis

It will be noted that this entire examination may be conducted *without the use of any equipment* whatever. An oscillometer provides helpful confirmatory evidence when properly used and when its readings are not overinterpreted It is recommended that the examiner take blood pressure readings in both upper and both lower extremities. Many cases of coarctation of the aorta have been missed because of the omission of blood pressure or oscillometric readings of the lower extremities. Even though careful palpation for arteries of the foot will, by absence of their pulsation, disclose coarctation in most cases, it is well to be doubly certain Observations of color of the skin are so important in these diseases that it seems appropriate to comment at this point on the mechanism of production of the color of the skin.

Mechanisms responsible for skin color.—The most important single factor in the color of the skin is the blood in the subpapillary venous plexus The plexus is made up of fairly wide channels in the deeper layers of the skin into which the superficial capillaries

and glomera drain. If the capillaries themselves are widely dilated, they may affect the skin color The quality of the blood which flows through the subpapillary venous plexuses also influences the skin color, for blood containing a large amount of oxyhemoglobin produces a bright red tint. The venous blood produces a darker hue, depending in part on the oxygen content of blood which has passed into the veins through glomera or congenital arteriovenous anastomoses and partly on the oxygen or lack of it in blood which has passed through capillaries. In general, the longer blood is in capillaries, for example in profound venous stasis, the darker will be its color and hence the color of the skin. With certain cardiac and pulmonary conditions which interfere with normal oxygenation of the blood there is also a tendency to a cyanotic hue. The skin depends also on the balance between the sympathetic and parasympathetic nervous systems which control the lumens of the blood vessels. This is especially true of the arterioles, which have a strong muscular coat and act as valves to the peripheral circulation. Strong stimuli such as fright, anger and cold may cause contraction of the arterioles, limiting sharply the amount of blood supplying the skin and producing definite pallor. This is accentuated to a pathologic degree in Raynaud's syndrome.

Occlusion of a major artery or spasm or organic blockage of many arterioles will, as previously mentioned, produce pallor in an extremity, even when the subject is supine. This is simply explained on the basis of inadequate arterial flow to the part, so that the subpapillary venous plexus is relatively empty. Elevation of the extremity greatly accentuates the phenomenon. Rubor is occasionally seen in the tips of the fingers or toes of an elevated extremity in the presence of organic arterial occlusion with infection. The explanation for this phenomenon is not clear It is possible that in an endeavor to secure an adequate blood supply minute vessels, including the glomera, are almost permanently abnormally dilated. (The temperature changes of the feet are discussed later.) Rubor that persists even on elevation, with a definite

increase in temperature, suggests a diagnosis of erythermalgia.

The patient may have mottling of the skin (discussed further in Chapter XIV). In some individuals it is so mild that it is probably normal, and in others it is so pronounced as to warrant consideration of a vascular disease. It is most marked in the skin of the arms and legs but sometimes involves other areas, notably the palms. Other individuals have marked rubor of the thenar and hypothenar eminences. The explanation is not clear, but the condition is often seen with such diseases as rheumatoid arthritis, pernicious anemia and liver disease

Throughout the examination thought should be given to evidence of edema. Although the commonest site of edema is the lower extremities below the knees, it may be found in any portion of the body Edema of the face and trunk is usually associated with generalized cardiac, nephritic or metabolic disturbances. Edema of the upper extremities may be associated with lymphedema or primary axillary venous thrombosis Edema of the lower extremities may be associated with cardiac and nephritic diseases and with protein deficiency From the vascular point of view the problem is primarily one of differentiation between blockage of the venous and of the lymphatic system Frequently both systems are involved It is important to note whether the edema is pitting or nonpitting in type A common error in testing for this is to apply the finger pressure too briefly. Pressure should be firm and prolonged for one to two minutes if necessary. Pitting edema can frequently be reduced by elevation of the extremities and other measures, whereas nonpitting edema caused by the proliferation of lymphoblasts and other connective tissue elements frequently can be reduced only by radical surgery in the form of a Kondoleon operation

It should be remembered that pitting edema of the extremities can be produced by constricting pressure proximal to the site of the edema This is commonly due to tight garments, especially

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girdles and garters, but we have also seen it as a result of tourniquets applied by individuals who have successfully used this method for malingering

Special Examinations and Tests of Status of the Circulation

The purpose here is to outline technics of study which will provide additional information regarding the status of the circulation in a part or in the whole body under examination. Certain tests that can be performed with equipment readily available in every doctor's office are emphasized and described in detail. Other tests, requiring specialized equipment or training, for the most part provide information of a research nature. Although information gained from them has been of great value in establishing basic concepts of the pathologic physiology of vascular diseases, they are rarely essential to the correct diagnosis and treatment of the patient with a vascular disease The complex tests are presented briefly in order to explain their function and methodology. For further details the reader should refer to original communications listed at the end of the chapter.

Color Variations on Postural Changes of the Extremities

A most useful observation which is available to all physicians and requires no apparatus is that of changes of color of the foot or hand following elevation and following dependency. For study of the foot the patient should be in the supine position with the foot at body level. In the absence of vascular disease, local infections or lesions or changes in the blood itself, the foot will have normal color and the balls of the toes a pinkish red color without pallor, marked rubor or cyanotic tints. Certain vascular diseases may cause pallor, excessive rubor or cyanosis even in the

supine position. Color changes are accentuated by the following postural changes.

The legs are first elevated from the horizontal to a 45 degree angle and observed for color changes. It is better for the examiner than for the patient to support the feet, since tension of the muscles of the abdomen and thighs may unduly fatigue the patient and cause muscular pressure on the vessels, changing the lumens of the potential vascular channels In the presence of occlusive arterial disease such as arteriosclerosis obliterans and thromboangiitis obliterans, the toes and feet will blanch unless most unusual collateral circulation has developed. In very early

or three minutes. Often it can be increased by having the patient move the toes and feet actively This rapidly empties the area of blood and new blood is slow to flow in. The degree of pallor may be indicated by + to ++++. Pallor may occur even in the presence of pulsating dorsalis pedis and posterior tibial arteries, and usually indicates the occlusion of arteries peripheral to the points of palpation This point is not generally appreciated by physicians, who often assume that all is well if they can palpate these two large arteries Marked pallor of both feet (++ to ++++) usually indicates disease Pallor of one foot in contrast to normal color of the other is to be regarded as highly presumptive evidence of definite circulatory impairment of the pale foot

The patient then lowers the feet to a position of dependency by hanging them over the edge of the examining table or bed (preferably while sitting up). Normal color should return within 10–15 seconds In the presence of occlusive arterial disease the toes and feet will become a very bright red, this may take several minutes. The color usually changes to a cyanotic hue. The change may be graded + to ++++ for the record.

Although very slight changes in color may be considered to be within normal limits, profound changes in color following postural changes should be considered among the most significant evidence of the presence of occlusive arterial disease Another example of the value of the test for color changes with changes of posture is the marked dusky cyanosis of the feet on dependency

which suggests venous pathology, probably occlusive, especially when elevation produces blanching only to what might be termed normal color. Color changes on dependency are also most noticeable when unilateral, indicating definite impairment of the circulation of only one extremity.

It must be remembered that some systemic diseases may be responsible for rubor, cyanosis or pallor of the skin of the extremities as well as elsewhere. These include polycythemia vera and methemoglobinemia, which may produce rubor, and cardiac and pulmonary conditions which produce cyanotic states associated with anoxia. Persons with a vasospastic diathesis, especially women who have never been athletic, may have cyanosis of the feet on dependency, as do patients with neurocirculatory asthenia. Profound anemia may cause severe pallor Argyria may be confused with cyanosis. In argyria one of the first places for the slate-blue discoloration to appear is in the nail bed. Deposition (silver sulfate?) begins as a small line like a crown around the distal edge of the lunula and extends gradually to involve the entire nail bed True cyanosis, on the other hand, involves the entire nail bed about equally. Therefore the presence of a crown on the lunula may aid in differentiation of early argyria from true cyanosis. This observation was first made by the author in 1934.

TESTS FOR INTERMITTENT CLAUDICATION

Intermittent claudication is one of the most common persisting symptoms of occlusive vascular disease. Characteristically, the patient complains that after he walks a certain distance pain develops in the muscles of his legs. That forces him to stop. After a few minutes of rest he can proceed approximately the same distance again. It is wise to establish a quantitative measure of this phenomenon so that the course of the condition can be followed with some accuracy. Barker and his co-workers at the Mayo Clinic have used a test whereby the patient walks at the rate of 120 steps a minute with an attendant who uses a stop watch to regulate the

speed. The time lapsing between the beginning of the test and the beginning of pain is known as the "claudication time" This test is sometimes inconvenient because of inclement weather and other reasons. Various types of ergometers have been developed to overcome this objection A simple one has been used in our clinic for several years.

The patient stands erect with his foot on a pedal which he presses down, thereby lifting a weight of 13.6 lb. (Fig 9) He does this at the rate of 120 times per minute until the onset of pain (claudication time) Those with serious occlusive vascular disease may only be able to carry out this procedure for 10 or 15 seconds before severe pain develops in the calf, whereas after successful therapy they may be able to continue for five or more minutes A normal individual may continue for five or even 10 minutes without evidence of severe fatigue

These attempts at quantitative evaluation are not beyond criticism but permit comparative analysis from a clinical point of view

OSCILLOMETRIC STUDIES

The use of an oscillometer is not essential to the diagnosis of most vascular conditions, but it is helpful at times in making certain that the examiner's palpating finger is not betraying him I have seen patients whose physicians claimed that they felt the dorsalis pedis artery but in whom it was possible to demonstrate, by means of an oscillometer, that there were no pulsations in major vessels below the knee. Such doctors, when asked to press their finger-tips against an inanimate object, have discovered such strong pulses in their finger-tips that they were not reliable as fine palpating organs In other patients it has been impossible to find the dorsalis pedis artery by palpation, yet oscillometric readings clearly demonstrated a strong pulse and an obviously major arterial pulsation in the foot

The level at which the major arteries are blocked can be determined by an oscillometer fairly accurately and more easily than by an arteriogram, although in some instances the arteriogram

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TESTS FOR INTERMITTENT CLAUDICATION

Intermittent claudication is one of the most common persisting symptoms of occlusive vascular disease. Characteristically, the patient complains that after he walks a certain distance pain develops in the muscles of his legs That forces him to stop. After a few minutes of rest he can proceed approximately the same distance again. It is wise to establish a quantitative measure of this phenomenon so that the course of the condition can be followed with some accuracy. Barker and his co-workers at the Mayo Clinic have used a test whereby the patient walks at the rate of 120 steps a minute with an attendant who uses a stop watch to regulate the

A number of types of oscillometers have been manufactured. Our experience with all known varieties of oscillometers has demonstrated the von Recklinghausen apparatus to be the most sensitive and durable. It is made in Germany. The Pachon oscillometer, made by the Boulitte Company of France, is satisfactory. The oscillometer consists of a pneumatic cuff connected by rubber tubing to a recorder with a sensitive diaphragm Pulsations against the pneumatic cuff transmit pressure to the capsule moving a needle across a dial which measures in units what is termed the oscillometric index. Different machines show considerable variation in response to a given pulsation. It is important, therefore, that the examiner be familiar with his equipment in order to evaluate properly the relative pulsations noted in one individual and to compare the readings for one individual with those for others. It should be understood that the oscillometer does not differentiate between organic occlusive disease and a vasospastic state which may be temporary The following readings are normal as measured by most oscillometers:

Lower Extremity		Upper Extremity	
Midthigh	4–16	Upper arm	4–16
Upper third of leg	3–12	Elbow	3–12
Above ankle	1–8	Wrist	1–10
Foot	0 2–1 0	Hand	0 2–2

It is important that oscillometric readings be performed in a warm environment, preferably above 70 F., so that vasospasm of the arteries caused by cold or chilling may not be a factor in the readings. The patient should be exposed to this environment for 30–60 minutes if he has just come from out of doors on a winter day. When in doubt, we customarily surround the patient with blankets and if necessary use hot water bags and heating pads to nullify the effect of chilling, nitroglycerin sublingually may increase pulsation in a vessel constricted by vasospasm

Various technics for recording the results have been utilized It is now common practice to consider as the oscillometric index of a given point, e.g, below the knee, the greatest swing of the

gives more precise information. The level is discovered simply by taking readings at various levels from the foot up over the ankle, at the midcalf, upper calf, level of the knee and at various levels

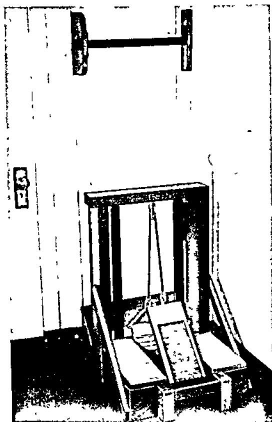


Fig 9.—Ergometer for measuring claudication time. Patient stands with foot of extremity to be tested on the treadle Pressing down, he lifts a 13 lb weight Pressure at regulated speed of 120 times per minute discloses the work necessary to produce claudication, and results can be compared with future performance.

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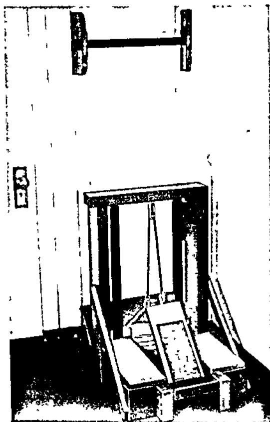


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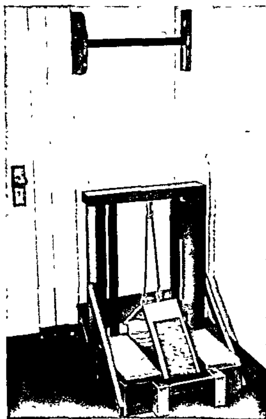
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Midthigh	4–16	Upper arm	4–16
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Above ankle	1–8	Wrist	1–10
Foot	0.2–1.0	Hand	0.2–2

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For observations of the skin temperature a small m mometer with a wide bulb has been devised. Howev oughly satisfactory thermometer of this type has not l oped because varying degrees of pressure against the a rise or fall of the mercury A more satisfactory a the potentiometer,* which indicates the temperature in degrees of fahrenheit or centigrade directly follow tion of a thermocouple to the skin (Figs. 10 and 11) ment known as Dermotherm† has been used with sat many workers There are several modifications of th apparatus.

Variations in the surface temperature, like oscillon ings, must be interpreted with caution There is a wic the surface temperature of the extremities of normal the accepted standard environment of about 25 C (7 40 per cent humidity, the surface temperature varies l 35 C. (73–93 F.) even after the subject rests under cont ditions for a long time The forehead, thorax and upp of the leg are, on the average, 7–10 degrees (C, warmer than the toes. The temperature of the fingers lies in the range of 32–35 C. (88–93 F) The temperat skin of the toes and of the muscles of the calf are related.

It has been demonstrated that the surface temperat extremities is greatly influenced by environmental tempe also by the basal metabolism. The temperature is also the ingestion of food, smoking, emotional stimuli and r factors. The humidity of the air within usual limits ha little influence on the skin temperature.

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* Leeds and Northrup Company
† Taylor Instrument Companies

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In summary, the oscillometer has been found to be a useful adjunct to our diagnostic procedures Its limitations must be clearly understood in order to avoid overinterpretation of its function

SURFACE TEMPERATURE

The surface temperature may contribute important evidence for the establishment of a diagnosis of peripheral vascular disease and the type in the individual patient. Perhaps the most significant observation, and one easily made, is that the temperature of one extremity is much lower than that of its counterpart, even though both have been exposed to the same environmental conditions. One or two fingers or toes may be definitely cooler than the other digits of the same extremity. These are important observations and indicate organic occlusive arterial disease or a vasospastic phenomenon such as Raynaud's

Clinically, the examination for surface temperature is relatively simple It is best that the examiner use the dorsal surfaces of his fingers distal to the first phalangeal joint. In most individuals this area is more sensitive to slight temperature changes than are the palmar surfaces of the finger-tips The dorsal surfaces of the fingers are slowly moved distally over the entire length of the extremity to the tips of the toes or fingers. In this way a zone of sudden change of temperature is easily noted Differences of far less than 1 degree (C) are determinable. If the temperature is much lower in one extremity than in the other this must be considered important evidence of a circulatory disturbance Comparison of the temperature of the soles should not be overlooked. If the temperatures of the feet or hands are markedly elevated above the anticipated levels one must consider erythermalgia, usually a bilateral or quadrilateral phenomenon Thrombophlebitis, lymph-

angitis and infections of various types also cause local increase in heat which is determinable by this method.

For observations of the skin temperature a small mercury thermometer with a wide bulb has been devised. However, a thoroughly satisfactory thermometer of this type has not been developed because varying degrees of pressure against the bulb cause a rise or fall of the mercury. A more satisfactory apparatus is the potentiometer,* which indicates the temperature of the skin in degrees of fahrenheit or centigrade directly following application of a thermocouple to the skin (Figs. 10 and 11). The instrument known as Dermotherm† has been used with satisfaction by many workers. There are several modifications of this type of apparatus.

Variations in the surface temperature, like oscillometric readings, must be interpreted with caution There is a wide range in the surface temperature of the extremities of normal persons In the accepted standard environment of about 25 C. (72 F.) with 40 per cent humidity, the surface temperature varies from 24 to 35 C. (73–93 F) even after the subject rests under controlled conditions for a long time The forehead, thorax and upper portions of the leg are, on the average, 7–10 degrees (C., 12–18 F) warmer than the toes. The temperature of the fingers ordinarily lies in the range of 32–35 C. (88–93 F) The temperatures of the skin of the toes and of the muscles of the calf are not closely related.

It has been demonstrated that the surface temperature of the extremities is greatly influenced by environmental temperature and also by the basal metabolism The temperature is also affected by the ingestion of food, smoking, emotional stimuli and many other factors. The humidity of the air within usual limits has relatively little influence on the skin temperature

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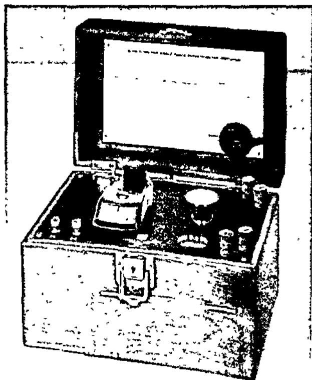
of the blood flow to the extremities but only an index of the blood flow to and through the skin and subcutaneous tissues. A single casual reading or series of readings of the skin temperature of the extremities probably provides little significant information except regarding differences in two corresponding areas on opposite sides of the body. However, tests for reflex vasodilatation have increased the value of surface temperature studies These studies can be carried out easily if the physician has the proper temperature recording equipment. They depend on the principle that when a normal individual places one extremity in very warm water, the opposite extremity will show a marked increase in temperature The following detailed test may be carried out

The temperature of the room should be approximately 21 C (69.8 F.). After the patient has been stabilized in this environment for 30–60 minutes, one or two extremities are immersed in water at 42–44 C. (107.6–112 F.). The patient is covered with blankets to maintain the heat. In normal individuals the un-immersed extremities will show a marked rise in the temperature of the digits, to a minimum of 34 C (93 F.) within 35 minutes Un-immersed extremities with deficient circulation will fail to respond with the normal rise.

A somewhat simpler test which is usually equally effective consists of the application of a heating pad over the abdomen while the surface temperatures of the tips of the extremities are followed.

It must be realized that occasional individuals who do not have occlusive arterial disease do not respond to these tests satisfactorily In such individuals it is necessary to use spinal or, in some, general anesthesia before the true vasodilatation response can be obtained

The explanation for reflex vasodilatation appears to be somewhat as follows Warm blood returns from the warmed extremity to the general circulation, thereby affecting the heat centers in the central nervous system. If the return is prevented by the use of a cuff proximal to the level of immersion of the extremity, there will be no reflex dilatation until the cuff is released Apparently the warm blood is the afferent limb of a reflex arc and the sympathetic system represents the efferent limb of the arc, producing



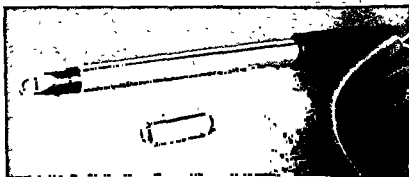


FIG 10 *(above)*.—Body temperature potentiometer indicator.

FIG. 11 *(below)*.—Thermocouple for determination of skin surface temperature. (Courtesy of Leeds and Northrup Co.)

of the skin as a result of anesthetization" The lower limit of this level, for the surface temperature of the great toe, is considered to be 31.5 C. (88.5 F) with room temperature at 20 C (68 F). The important observations are the maximal level to which the skin temperature rises and the comparative temperatures of the skin of the suspected and the normal limbs.

The procedures involving detailed study of the surface temperature under various conditions of anesthesia, while of interest and sometimes of help, are generally not vital to the diagnosis of a peripheral vascular disease.

Vasomotor index.—This index, described by Brown and his associates, is a figure which indicates the increase in cutaneous temperature of the toes or fingers as compared with the increase *in oral temperature following the injection of typhoid vaccine* It equals the increase in skin temperature minus the increase in mouth temperature divided by the increase in mouth temperature. This gives some indication of how circulation can be increased by fever but contributes little more than can be obtained by measuring the maximal level to which the temperature of the finger digits rises following an injection of typhoid vaccine. The normal maximal rise should be over 31 5 C. (88.5 F.) if the oral temperature indicates 2 or more degrees (C.) of fever.

Histamine flare test.—Mention should be made of the histamine flare test, which has enjoyed some popularity.

A 1:1,000 solution of histamine acid phosphate, with 0 5 per cent Chloretone as preservative, is used. The patient should be completely relaxed. One drop of histamine solution is placed at each of the following levels: the dorsum of the foot, the outer leg 3 in. above the ankle, the outer leg 3 in. below the knee, and the thigh 2 in above the patella. Multiple inoculations are made over these spots by pricking the area with a fine needle to penetrate the skin, with care to avoid drawing blood. Observations are made at 2½ and 5 minute intervals The development of a wheal and a flare zone of erythema is noted In normal individuals the wheals appear in 2½ minutes and are completed within 10 minutes

striking reflex dilatation if the integrity of the vascular system is intact.

ANESTHESIA AND DRUGS AS DIAGNOSTIC AIDS

Anesthesia.—It is common knowledge that widespread vasodilatation of the skin follows general anesthesia. For example, nitrous oxide-oxygen anesthesia will within 15–20 minutes produce maximal vasodilatation, with a rise of temperature of the entire surface of the body to a high level (33.9–35.6 C.; 93–96 F.). Sometimes it is necessary to produce profound anesthesia by ether to secure maximal vasodilatation. If the arteries of an extremity are sufficiently involved by an occlusive arterial disease, the temperature of the affected area will not reach the high level achieved in other portions of the body and other extremities.

Probably the most commonly employed test using an anesthetic agent is the injection of procaine, or a similar substance, in the area of the ganglions of sympathetic nerves supplying an extremity. This should be carried out by one skilled in the procedure. Even then, although a sharp rise in the temperature of a limb signifies release of spasm, when no temperature rise occurs it is difficult to be certain whether this is due to the presence of occlusive arterial disease or to failure to infiltrate the proper area.

A more certain test for the lower extremities alone is that by means of spinal anesthesia. It is also possible to test for a local circulatory fault in the foot by injecting 10 cc. of 1 per cent procaine into the posterior tibial nerve through the fascia through which the nerve passes just below the internal malleolus behind the posterior tibial artery. In 10–15 minutes the vasoconstrictor mechanism is relaxed and, normally, marked warmth is apparent. This is limited to the anesthetized skin of the heels, toes or plantar surfaces of the toes and the dorsum of the foot. For studies regarding these phenomena in relation to anesthesia, we are indebted to Morton and Scott, who stated that "the normal vasodilatation level indicates the maximum value for the temperatures

Another type of arteriography involves the use of a radiopaque substance for intra-arterial injection. For this purpose Skiodan, Diodrast and Thorotrast have been most used The injection of Skiodan is so painful that it is not recommended A 35 per cent solution of Diodrast is more satisfactory and in most instances can be injected directly into the artery without causing undue pain or arteriospasm. It is fairly satisfactory as an opaque substance Seventy per cent Diodrast has also been used.

Thorotrast, which is stabilized thorium dioxide solution, gives the best visualization of the vascular tree. It is virtually painless unless injected by mistake into the surrounding tissues No immediate generalized toxic effects have been reported Roentgenologists have been slow to utilize this substance for fear of the radioactivity attributed to the thorium dioxide, but more than 10 years of experience with this substance has convinced me that the risk has been greatly exaggerated, is actually minimal and has failed to justify the fears expressed. A very few cases have been reported in which there has been a suggested damage from radioactivity secondary to the use of this substance Some individuals died, most of them of liver carcinoma or other serious disease for which thorium dioxide had been administered as a diagnostic procedure We observed between 300 and 400 patients who received injections of this substance more than 12 years ago without encountering a death which could be attributed to it Patients have been reported to be in good health 15–17 years after receiving 75 cc. of Thorotrast for hepatic and splenic pathology. Favorable experiences have been reported by Yater, Allen and others The risk is, in our experience, less than that with Diodrast, from the injection of which numerous deaths have been reported. The number is small, however, in view of the many patients who receive Diodrast for renal and other roentgenology

Technic.—The patient lies on the x-ray table, the film under the outstretched extremity. Although local anesthesia has been recommended, it has not been found necessary in our clinic. It is doubtful

Kramer believes a subnormal reaction to be evidence of impaired circulation This test is claimed to be of some aid in evaluating the circulation in patients thought to have had some re-establishment of collateral circulation which is not measurable by oscillometric studies. We have not found it to be of vital importance in the study of patients with vascular diseases

A similar test using saline intradermally has been advocated, but we have not adopted it because we did not feel that it gave sufficiently accurate information.

ANGIOGRAPHY

Arteriography.—The simplest form of arteriography is the taking of x-rays by the soft tissue technic to determine whether the walls of the arteries are calcified to any degree. If an extremity is to be studied it is recommended that the entire limb be subjected to this searching type of examination, for frequently the calcification is patchy and may be missed if only a small portion of the arterial tree is x-rayed This is particularly true of the vessels of the lower extremities, in which pelvic arteries as well as the entire tree should be studied *It is important that the roentgenologist take lateral views of the flexed knees, because anteroposterior views often fail to show arteriosclerotic plaques directly behind the patella* In diagnostic evaluation it is of interest to know whether there is any calcification and, if so, the approximate amount For example, it may aid in the differential diagnosis of arteriosclerosis obliterans and thromboangiitis obliterans in individuals in the fifth and sixth decades It should be understood, however, that the amount of calcification is not an index of the patency of vessels. I have seen patients with so-called "pipestem" arteries extending the entire length of the legs and into the feet, despite which the arteries were fully patent as demonstrated by palpation and oscillometric readings. In other cases a small, rather inconspicuous calcified plaque has been the site of a thrombus which occluded the artery.

it was due to the fact that injection was made by error into the veins and the material was carried proximally out of the extremity instead of distally into the peripheral arteries.

The information sought with this method includes the following main features: (1) in the lumens of the arteries, evidence of marked irregularity, reduced caliber or complete occlusion, (2) the degree of collateral circulation and its general distribution, (3) congenital variations, including changes in location of vessels and arteriovenous anastomoses; (4) the presence of aneurysms and arteriovenous anastomoses due to disease or injury, and (5) the presence and general configuration of vascular tumors

Normally, the arteries show a smooth contour and gradual diminution in size as they progress distally. In the hand the volar arch is visualized rather clearly joining the radial to the ulnar artery, and the branches may be seen extending to each of the digits. Small arteries are frequently visualized as a fine communicating network. Spasm of the vessels usually results in rather uniform, smooth diminution in caliber which may be marked enough to cause complete obliteration, although it sometimes produces what appears to be an abrupt occlusion of an arterial segment.

Occlusive arterial disease causes irregular or "moth-eaten" patches of narrowing or rather abrupt complete occlusion of the involved vessels. In thromboangiitis obliterans it is difficult to predict where the patchy occlusion may occur, but most frequently one first sees the typical moth-eaten appearance involving the distal digital peripheral blood vessels This later extends proximally up the arteries. The venous channels also are frequently obliterated in thromboangiitis obliterans, in fact, venous damage may appear first This important point is not sufficiently appreciated.

In arteriosclerosis obliterans a primary occlusion may occur at any level and frequently involves a major vessel midway along its course. For example, the popliteal and dorsalis pedis arteries are common sites of blockage. The arteriogram clearly shows the

that the discomfort of the anesthetic needle is much less than the discomfort of the needle to be used for penetration into the artery. Nor has it been found necessary, with one exception, to cut down on an artery. The artery, for example the femoral, is carefully palpated, and the second and third fingers of the left hand hold it in position while the needle fixed to a 30 cc. syringe containing the opaque medium is guided into the lumen. An 18 gauge 2 in. needle is best for this purpose. In most instances the injection of the femoral artery just distal to Poupart's ligament is a relatively simple procedure, injection of the radial artery for visualization of the hand is more difficult.

It is important to make certain that the needle is in the vessel by pulling outward on the plunger before starting the injection. It is equally important that the needle be in the artery and not in the vein. This can be ascertained by noting that on entrance into the lumen of the artery bright red blood rushes back into the syringe with a pulsating rhythm, whereas on entrance into the vein dark blood flows sluggishly into the syringe Ordinarily 12.5–15 cc of Thorotrast is sufficient for a single injection The roentgenologist must be ready to take pictures at the exact second during which the portion of the vascular tree under study contains the Thorotrast. Thus, frequently the x-ray exposure should be made during the last two or three seconds of injection if one is studying the arteries. Serial exposures may be taken during the next few seconds to catch the Thorotrast as it proceeds distally to the digits and then returns through the venous channels

It is apparent that the technic of injection and the interpretation of the films are problems for specialists The following points regarding interpretation may, however, be briefly reviewed. To interpret arteriographic studies properly, one must be familiar (1) with the normal vascular structure, including the main vessels and the most common branches; (2) with the unusual possibilities from the point of view of spasm of the vessels and of aberrant locations of the vessels, and (3) with the limitations of the method, including the errors arising from improper injection of the material, incomplete filling of the vascular tree and improper timing of the x-ray exposure. For example, the absence of Thorotrast in the arterial tree of a limb has been interpreted as demonstrating the presence of serious vascular disease, whereas actually

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abrupt obstruction of the major vessel and, in many cases, the collateral circulation of fine vessels branching from the proximal portion and extending parallel to the original course of the artery. The collateral vessels may terminate independently or by rejoining the main vessel distally. In fact, the distal end of the main arterial tree may be filled with radiopaque substance as a result of effective collateral circulation. Collateral vessels may proceed through tortuous routes, but their general function is to re-establish the balance of circulation in the tissues, peripheral to the blockage. In arteriosclerosis obliterans, occlusion may not be complete, but damage may be apparent from the very irregular contour of the vessel caused by cholesterol and calcium plaques. In cases of arteriosclerosis evidence of aneurysms is not uncommon. In some instances these rupture, producing false aneurysms. This is most common in the popliteal space. An excellent example is shown in Figure 74 (p 304).

The picture of arteriovenous anastomosis is noteworthy for the fact that the radiopaque substance, instead of passing rapidly down the limb in the main artery or arteries, is diluted by passage through shunts directly into the venous channels, and these are noted to be returning the opaque substance seconds earlier than is normal At the site of the anastomosis there are apt to be a number of tortuous vessels. In large vascular tumors, as well as some types of arteriovenous anastomosis, pooling of the opaque substance may be striking In other cases the tumor may be clearly outlined by innumerable branches which stand out because of the radiopaque substance they contain Information obtained from arteriography at times has real value to a surgeon, contemplating an exploratory procedure. The following instance is an example.

A patient was referred with a diagnosis of probable osteogenic sarcoma. A hard mass palpated in the popliteal area was nonpulsating and

period of some months blood had clotted into a thick sheath covering the aneurysmal sac. It became more firmly packed with each pulsation, which forced the blood against this sheath Operation confirmed this interpretation and a large mass of firm clot material was removed A reparative operative procedure was carried out by suturing a slit ½ in long in the popliteal artery and the leg was saved, instead of being amputated above the knee as had originally been intended

Venography.—This may be carried out by two methods In the first, the radiopaque substance is injected into the arteries supplying the veins to be studied and the x-ray exposures are timed to catch the material as it flows back toward the venous channels This method requires expert co-operation by the roentgenologist It may be controlled to some degree by using a sphygmomanometer cuff, inflating it above the systolic pressure and deflating it periodically to the diastolic pressure for two to four heart beats at a time This requires experience by trial and error to perfect the technic for each team of operators. Frequently this method fails to be entirely satisfactory because the solution becomes too diluted during passage into the venous channels.

The second technic is to inject the radiopaque substance directly into the lumen of the vein under study An example is the injection of radiopaque substance into the basilic vein to determine the site or presence of an axillary venous thrombosis. If the axillary vein is blocked there are marked dilatation and tortuosity of collateral veins extending over the deltoid and pectoral areas If the axillary subclavian vein is open and functioning normally the radiopaque substance passes rapidly and smoothly through the main channels and few branches are noted The valves of the veins are frequently distinguished by small saccular arrangements at intervals along the venous channels Venography has also become a popular aid to the diagnosis of acute thrombosis of the veins of the lower extremities

For this purpose, 20 cc of 35 per cent Diodrast or 12 5–25 cc of Thorotrast is injected into a vein of the dorsum of the foot or ankle

An x-ray exposure is made 20 seconds and again 30 seconds after completion of the injection. If possible one should use a long narrow film measuring 7 × 17 in. for study of the foot, leg and knee and a plate 14 × 17 in for the thigh

Bauer, and DeBakey and his associates consider it possible to determine the presence of thrombosis of the deep veins if there is an indication of incomplete filling of the deep veins and dilatation of the superficial veins They feel that this method of venography is of great value in establishing the diagnosis. Other workers do not unanimously concur with this opinion. In my experience the picture frequently is confusing. There are instances in which thrombosis has been proved to exist and venography failed to indicate it Thromboses large enough to produce clinically recognizable pulmonary emboli may come from branches rather than from the main veins, they may come from veins elsewhere in the body, and they may have been present in the veins of the legs and have broken loose in their entirety. Venography is an optional procedure which may have some value in certain cases, may be confusing in others and is not essential to the establishment of the diagnosis of thrombophlebitis of the veins of the legs in a large proportion of cases.

Visualization of the great vessels of the heart.—Extensive work has been carried out to perfect methods for visualizing the great vessels and the various chambers of the heart by means of radiopaque substances In this country Robb and Steinberg have made outstanding contributions. The following structures have been visualized: the superior vena cava and its tributaries; the four chambers of the heart and its walls; the ventricular septum, the pulmonic and aortic valves and their respective sinuses; the entire pulmonary circulation; the thoracic aorta, its wall and many branches, and the abdominal aorta (Figs. 12-16). It is frequently of great value in the study of congenital malformations of the heart and great vessels

Twenty-five to 40 cc of 70 per cent Diodrast is injected rapidly



FIG 12.—Normal heart, frontal view, 2½ seconds after beginning of injection of Diodrast Medium is entering left subclavian and innominate veins, superior vena cava is filled Right auricle and ventricle and main stem of pulmonary artery are opacified (This and Figs 13–16 reproduced by courtesy of Dr I Steinberg)

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Twenty-five to 40 cc. of 70 per cent Diodrast is injected rapidly



Fig 14—Normal heart, frontal view, seven seconds after beginning of injection Left ventricle, aorta and its branches in the neck are opacified Note thickness of left ventricular wall.

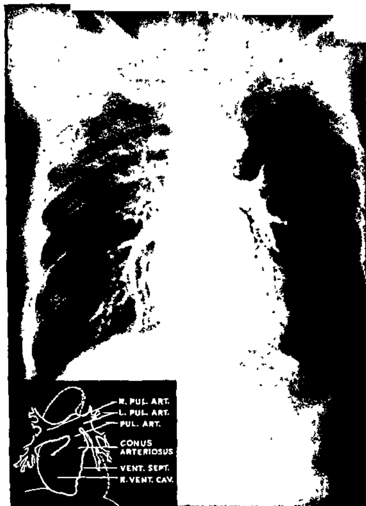


FIG 13.—Normal heart, frontal view, three seconds after beginning of injection. Right auricle is empty; right ventricle, pulmonary artery, right and left branches and their subdivisions are filled with Diodrast



FIG 16—Subclinical coarctation, left oblique view, in woman aged 35 Left ventricle and entire thoracic aorta are opacified Note marked narrowing of lower thoracic artery and dilated proximal portion containing calcium in wall



FIG. 15 —Coarctation of aorta, left oblique view, in woman aged 37. Lef ventricle, thoracic aorta and particularly the dilated innominate and left commoı carotid arteries are opacified Note point of coarctation and dilated descendin; aorta.

PLETHYSMOKYMOGRAPHY

The plethysmograph or plethysmokymograph has a limited place in the clinical study of individuals with peripheral vascular diseases. Its chief value is in the study of physiologic and pathologicophysiologic processes in the laboratory. The usual apparatus consists of a leakproof rigid container which is arranged to enclose a portion of an extremity and is connected to a recording device activated by changes of pressure within the plethysmograph The changes of pressure are produced by changes in volume of the enclosed portion of the extremity. Various experiments have *demonstrated changes in the volume of the extremities on exposure* to cold and to heat, on administration of drugs, etc

The recorder may write on a smoke drum or reflect a recording beam of light on photographic paper The increase of volume per unit of time is assumed to be an indication of actual blood flow, called the flow curve The publications of Abramson, Lampson, Freeman, Burch and many others give details of the procedure

Plethysmography of single digits of the hands or feet has been used Although the results are of interest, and may be of value, it should not be forgotten that each test shows only the response for the single digit being tested and that generalizations regarding the peripheral circulation—even as they may apply to the whole hand or foot—are fraught with serious risk of error.

OXYGEN CONTENT OF PERIPHERAL BLOOD

The saturation of oxygen in the arterial blood is normally between 93 and 98 per cent. The saturation of venous blood, however, varies considerably. Pease found that the saturation of the venous blood of the arm under basal conditions is 68.2 per cent with a range of 25–85 per cent. Thirty per cent of the *observations fell outside the range of 60–85,* which is frequently considered to be within normal limits. Reports on whether there is an increase or a decrease in the oxygen content of the returning

through a suitable vein at the elbow. Timing for x-ray exposure must be carefully planned in order to catch the contrast medium at the structures which it is desired to study. For example, the superior vena cava and its tributaries in the right atrium may be photographed approximately 1½ second after the injection is begun, the right ventricle and pulmonary tree in 3 seconds, the pulmonary veins and left atrium in 6–8 seconds and the left ventricle and thoracic aorta in 8–10 seconds

There have been severe reactions following the use of Diodrast. Some patients experience dizziness, weakness, nausea and occasionally severe vomiting, sweating, pallor and hypotension for two or three minutes These reactions are treated with epinephrine. Numerous deaths have been reported and we have seen several patients in whom thrombosis developed after having an arteriogram.

This technic requires experience, great care and excellent teamwork by the physician and the roentgenologist Its use is not recommended except under the most favorable conditions. The reader is referred to the monograph of Dotter and Steinberg and the reports of others for exact details of the technic.

INFRA-RED PHOTOGRAPHY

The value of infra-red photography in the study of peripheral vascular diseases can be simply stated It provides a permanent record for the patient's file or a means for the production of lantern slides or illustrations of the venous pattern of the veins just beneath the skin. Only rarely will it portray any veins which cannot be seen by the naked eye It is often used for the permanent recording of the collateral circulation of the deltoid and pectoral region in cases of axillary venous thrombosis and of venous obstruction due to mediastinal tumors. It is also used to record the collateral venous circulation of the abdomen when the inferior vena cava or the portal system is obstructed, and of the legs when there is obstruction due to thrombophlebitis. Infra-red photography is a good means of recording the status of livedo reticularis

of view both of the constituents of the blood and of capillary fragility per se.

Various tests from the time of Bier in 1909 to the present have been devised to provide some indication of increased fragility of the capillaries. These tests can be divided roughly into those based on the principle of positive pressure, induced by a tourniquet, and those based on the principle of negative pressure, induced, for

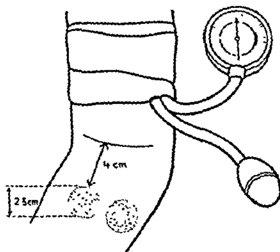


FIG 17—Standardized technic for positive pressure test of capillary fragility (Wright-Lilienfeld modification of Rumpel-Leede test)

example, by a small cup in which negative pressure or suction is produced over an area of the skin The Rumpel-Leede method, based on the principle of positive pressure, or the tourniquet procedure, has been modified by Hess and Fish, Gothlin, Wright and Lilienfeld and others A simple test which requires no special apparatus, but can be performed with a sphygmomanometer, and gives in a general way a quantitative measurement was described by Wright and Lilienfeld

Two circles 2.5 cm. in diameter, the uppermost edge of which is 4 cm. below the crease of the elbow, are drawn on the inner aspect of

venous blood in cases of arteriosclerosis obliterans and thromboangiitis obliterans are confusing. These readings are, therefore, probably not really of clinical importance.

The determination of the oxygen content of the venous blood is, however, of value in some cases of *arteriovenous anastomosis*. It is not always necessary to subject the blood to a chemical test to determine the oxygen saturation, it being sufficient to compare blood from the veins of both arms or legs if one is thought to contain an arteriovenous anastomosis In numerous instances the blood from the vein of one arm has been bright red, whereas blood from the vein of the other arm was normal venous color, many shades darker. In other words, by rapid passage of arterial blood into the venous channels without exposure to the demands of the tissues, the oxygen content was kept high, and this blood mixed with the returning venous blood produced a red color abnormally bright for venous blood. The diagnosis can frequently be established by this means The physician merely withdraws 10 cc. of blood from each arm or leg, puts the samples in separate test tubes and examines the tubes in a good light. If chemical studies are to be made, blood should be taken in such a way that the oxygen is not lost before the examination is complete Usually the blood is taken and kept under oil until tested

Verification of the diagnosis of arteriovenous anastomoses, especially in the presence of numerous small fistulas which do not produce a bruit, constitutes the main value of the oxygen studies

CAPILLARY RESISTANCE AND FRAGILITY

In the course of examination of a patient with vascular diseases or, indeed, of patients generally, numerous petechial spots or other evidences of purpuric manifestations are frequently noted The most common site of multiple petechiae is the distal half of the legs Curiously, the evidence of capillary hemorrhage is frequently overlooked Any manifestations of purpura or petechial bleeding constitute an indication for further study, from the point

In this method a small glass cup with a diameter of 1 cm. and with the edge turned at a right angle for 8 mm. is connected by a rubber tube to a manometer and syringe. The cup is applied to the outer section of the arm or any other portion of the body surface, and suction of any amount is made by means of the syringe The least negative pressure which, *applied for one minute, will produce microscopic petechiae* indicates the resistance of the capillaries.

Daldorff reported great variations in 251 subjects who were not suffering from any disease known to produce a hemorrhagic diathesis, petechiae being produced by 10 cm to as much as 50 cm Hg negative pressure This Daldorff himself described as a serious limitation to the use of the test He found the average in healthy adults to be in the range of —20 to —35 cm Hg Values of less than —20 cm were considered to be abnormal

There has been some criticism of the use of capillary fragility tests One criticism has been based on a lack of understanding of their function They give a definite answer to one question, namely, Are the capillaries more fragile (less resistant) than normal? *This information is very important.* It may be the first step toward the diagnosis in many cases and is frequently missed when a fragility test is not undertaken Such a test does *not* tell the physician why the capillaries are abnormally fragile any more than the finding of high blood pressure in a patient indicates why the pressure is high. The physician must search further for the underlying factors These may be vitamin C deficiency, streptococcus infections ranging from scarlet fever to subacute bacterial endocarditis, blood dyscrasias, malignant hypertension, arsenical poisoning, among many conditions. Another criticism has been based on the fact that the difference of a small number of petechial hemorrhages is not significant; small variations are unimportant in most biologic tests Serious consideration need not be given to the difference between 40 and 50 petechial spots per circle when the test is performed according to the first technic described here. But the difference between 10 and 50 or 100, as is frequently noted, is certainly significant.

the forearm (Fig 17). Any skin blemishes within these circles which could possibly be confused with petechiae are marked with ink. The *cuff of a blood pressure manometer is then applied* as usual around the arm and inflated to a pressure midway between the patient's systolic and diastolic blood pressure The pressure is maintained for 15 minutes and then released Five minutes after the cuff is released the number of petechial spots within the circles is counted with the naked eye and the average count in the two circles is taken as the result of the test *The spots are more easily counted if each is covered by ink from a pen*-point as it is noted.

Large clinical experience with this test for 12 years indicates that patients with normal capillary fragility will have 10 or fewer petechial spots There is a marginal value between 10 and 20 *Twenty spots or more definitely indicate an abnormal condition.* Counts of the capillary loops differ considerably in different areas of the skin The use of the area at the elbow crease, as advocated by Gothlin and Griffith, is in our experience subject to considerable error, because there is a great variation in the number of capillaries along the elbow creases in different individuals Also, some have one and some three elbow creases. Because the variation is reduced as one proceeds distally for about 4 cm, that area is suggested for the test

In some individuals in whom the fragility is markedly increased, countless petechial hemorrhages will be produced within 7½ or even five minutes In such instances the test can be discontinued and subsequent tests performed on the same time basis until, following therapy or in some cases spontaneously, the number of hemorrhages is reduced to a point where the 15 minute test becomes feasible. Tests may be performed every four days on alternate arms to allow eight days for healing. This is a *simple* test which, when positive, definitely indicates a pathologic state, although the underlying condition responsible for the capillary fragility is not always clear. This will be discussed later.

In 1933 Daldorff described a method for determining capillary fragility based on negative pressure.

In this method a small glass cup with a diameter of 1 cm and with the edge turned at a right angle for 8 mm is connected by a rubber tube to a manometer and syringe. The cup is applied to the outer section of the arm or any other portion of the body surface, and suction of any amount is made by means of the syringe. The least negative pressure which, applied for one minute, will produce microscopic petechiae indicates the resistance of the capillaries.

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In most cases in which fragility is due to vitamin C deficiency, the response to large amounts of vitamin C administered orally, or in some cases by necessity intravenously, is frequently astounding and constitutes one of the most satisfactory therapeutic responses in medicine (Fig 18). The early reports of striking reduction in capillary fragility following the use of rutin in doses of 20–40 mg. two or three times a day have not been confirmed Studies using doses up to 600 mg. three or four times a day are

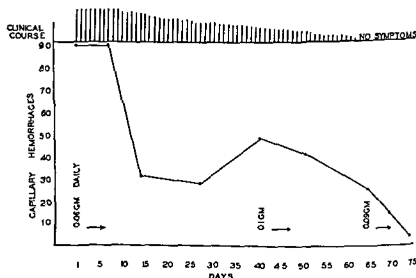


FIG 18 —Response to vitamin C therapy of capillary fragility due to vitamin C deficiency.

under way in our laboratory, but the data do not yet justify final conclusions.

The indications for a positive pressure test should constantly be borne in mind during a physical examination. Because no special equipment is needed, this simple test is readily available to every physician.

The negative pressure method has the advantages that the equipment, though special, is simple and that the test can be done

at frequent intervals because the cup can be applied over many areas of the body surface. Warning should, however, be given in this connection. The counts of capillaries of the skin in different portions of the body surfaces vary appreciably. This affects the number of potential petechial spots which can be produced in the respective areas. In order that the results of several tests may be compared, it is necessary to use comparable areas of the body surface for study. This point has been too frequently ignored by those using the method.

CAPILLARY MICROSCOPY

The circulation of the capillaries has long challenged the imagination of investigators Malpighi and Leeuwenhoek as early as

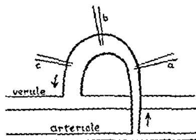


FIG 19.—Landis' points for reading capillary pressure

1686 studied the capillary circulation in the mesenteries and bladders of frogs, the tails of fish and the wings of bats From that time forth many workers studied the capillaries of various lower animals. In the last quarter of the nineteenth century numerous attempts were made to study human capillaries, with rather meager results. At the turn of the century, with the improvement in the technic of microscopy, these studies became more feasible Progress in the field is due to the labors of many workers, among whom were Spalteholtz, Heimberger, Lombard, Weiss and Muller, Boas, and Brown Krogh greatly stimulated work in this field by the

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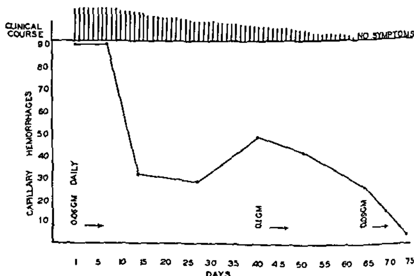


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associated with the pulsation of blood through the finger. For this reason we use a plastic material for embedding the finger firmly and the type of microscope which can be moved across the field with a ratchet and pinion system. A drop of cedar, mineral or castor oil is applied to the skin at the base of the finger-nail, and a beam of bright light projected from an arc light through a

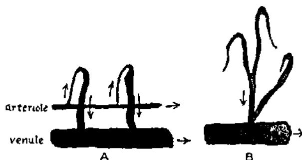


FIG 21—Different types of arteriole capillary-venule patterns

water bath and green glass filter is focused on the skin to illuminate the capillary loops properly The use of the method and its interpretation are, for the most part, reserved for workers making special studies in this field. A few comments may, however, be made regarding the significance and interpretations made available by the use of this technic.

Ordinarily, in the normal adult the whole field has a pinkish background in which the bright red capillary loops emerge in a form resembling hairpins which may be twisted or bent back on themselves (Fig. 21). In the background are seen the darker venous channels into which the venous limbs of the capillaries drain Focusing on a single capillary will show the blood moving through the capillary loop. The blood proceeds through the arterial limb distally and returns through the venous limb and venules The flow is rarely steady and uninterrupted. Cells advance in groups, flowing for a few seconds and frequently stop-

publication in 1922 of his monograph, *The Anatomy and Physiology of the Capillaries.* Richards, Lewis, Danzer and Hooker, Landis, Crawford and Rosenberger, Duryee and Wright, and Brown and Allen published variations in procedure and described their results. Landis made a significant contribution when he

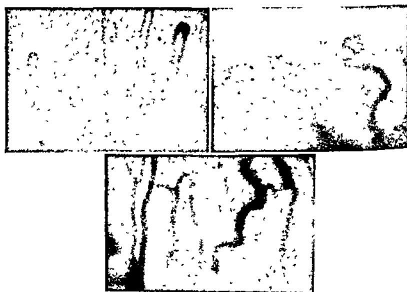


FIG. 20—Intracapillary anastomoses.

catheterized human capillaries and measured the pressure at various points, thus demonstrating the downward gradient of pressure within the capillary loops (Fig 19).

In our laboratory we have used the Leitz Ultropak system, by which it is possible to photograph capillary loops of the nail fold for a permanent record (Fig 20). It is difficult to draw conclusions regarding the significance of changes of capillary loops, their appearance or the rate of flow of the blood through them The difficulty is accentuated by the tendency in the patient to develop during the test either a fine muscular tremor or one

which the flow is stopped in a given curve is noted. The average of 10 such counts in the most prominent capillaries which are present at all times is considered the flow-test figure for that particular trial. Under average normal conditions the blood of an individual ceases to flow for a total of 10–20 seconds out of two minutes. However, in the presence of vascular spasm the flow may be interrupted for the entire two minutes or longer. Such an observation is regarded as significant and requires further study to determine the cause.

Flow may be influenced by many factors. Fever and increased temperature may accelerate the flow, whereas spasm due to cold or excitement may retard the flow. My co-workers and I have studied the capillaries in many diseases and have summarized the opinions of others regarding what one may anticipate in the presence of certain underlying conditions. With marked cardiac decompensation the rate of flow is frequently found to be slower than normal and to have longer intervals of cessation of flow. Changes had been reported in the presence of acute nephritis, although we could not substantiate morphologic changes in this condition. If the blood pressure was increased, there was frequently an increase in rate and constancy of flow. In hypertension, regardless of the cause, there appears to be an increased rate of flow. Most workers agree on this point. Using the two minute flow test, we found that the flow rarely stopped for longer than four or five seconds in the presence of definite hypertension. We did not note any unusual degree of tortuosity in the presence of arteriosclerosis. In polycythemia vera the limbs of the loops appear to be straight but filled and bulging with cells which move rather *sluggishly* through the lumen. In contrast, in a patient with relative polycythemia secondary to a congenital heart condition (8,540,000 red blood cells and a hemoglobin content of 111 per cent) markedly tortuous capillaries were observed.

The capillaries in Raynaud's syndrome have been described by many workers. Characteristically the arteriolar limb is moderately

ping, to proceed again as the pressure increases behind them. The walls of the capillaries in the human nail bed are more difficult to visualize than those in the mesentery of the frog, where trans-illumination can be used. What the observer actually sees is the column of cells. At times they proceed so rapidly that individual

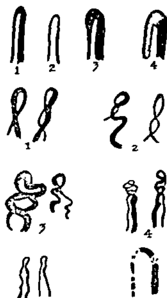


FIG 22.—Common morphologic variations in capillaries of human nail fold. Lowest line represents the "moth-eaten" capillary in arteriosclerosis and a capillary with breaks in the column of cells which are filled with serum

cells cannot be distinguished. There is a great variation in the diameter and degree of tortuosity of the capillaries in a single individual and indeed in a single nail bed. In general the arterial limb is slightly narrower than the venous limb.

To provide a roughly quantitative measurement we suggested some years ago the so-called "two minute flow test." A capillary is observed for two minutes, and the number of seconds during

which the flow is stopped in a given curve is noted. The average of 10 such counts in the most prominent capillaries which are present at all times is considered the flow-test figure for that particular trial. Under average normal conditions the blood of an *individual ceases to flow for a total of 10–20 seconds out of two* minutes. However, in the presence of vascular spasm the flow may be interrupted for the entire two minutes or longer. Such an observation is regarded as significant and requires further study to determine the cause.

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dilated, but the venous limb may be markedly enlarged, frequently being many times normal size. At room temperature and with *freedom from nervous tension the patent arterioles* are not in spasm The flow is nevertheless sluggish and there are often prolonged periods of stasis. Extravasations of blood into the surrounding tissues are frequently seen As the phase of spasm appears the arterioles apparently contract, reducing the blood flow. This results in loss of red blood cells from many capillaries as they drain into the venules, and hence the capillaries become invisible. Movement of the blood can then not be seen, the pallor of the skin becomes pronounced and an incision of the skin at that time may produce little or no bleeding. The phase of cyanosis is entered upon; intermittently clumps of cells are admitted, but their color appears to be darker than the average normal. With the release of arteriolar spasm, when the phase of hyperemia supervenes, the capillaries become engorged, the blood flow is suddenly and rapidly restored, and the color of the blood and the skin becomes bright red The picture of Raynaud's syndrome is perhaps the most characteristic observed by capillary microscopy.

When scleroderma develops, with or without Raynaud's syndrome, visualization of the capillaries becomes very difficult They appear to be obscured by a film or cloud, probably due to development of excess collagenous material in the skin When the flow can be seen it is usually slow and the blood frequently cyanotic.

The long-recognized tendency of blood cells to clump together, forming in some instances a block in a small vessel or moving in a mass, has been labeled "sludging." This has been observed in many patients and a wide variety of conditions, but its significance is not clear. This is especially interesting as it occurs in patients with cryoglobulinemia when the temperature of a distal part is lowered below a critical point for the precipitation of the cryoglobulin—usually 37 C. (98 6 F).

Many other vascular conditions are associated with changes of the capillary activity, but little additional information of clinical value is to be gained by the microscopic study of the nail fold capillaries. They represent only a minute portion of the capillary circulation and seldom provide information of key importance about disease processes. Such studies have helped to clarify certain problems and represent a limited but interesting form of study of the circulation. They are not, however, essential for the clinical diagnosis or treatment of the majority of patients suffering from peripheral vascular disease.

CIRCULATION TIME

The circulation time may be defined as the time required for the blood to flow from one point in a vein to certain other points in the circulatory tree If the blood flow is retarded, the circulation time is prolonged, and if the flow is accelerated the circulation time is shortened.

Various methods and substances have been used in the study of circulation time. The technic most often used has measured the time of blood flow between the median basilic vein and the tongue or portions of the brain Substances used have included compounds of potassium cyanide, certain radioactive substances, calcium salts, magnesium sulfate, saccharin, ether, sodium cyanide, histamine and dehydrocholic acid For example, the injection of a solution of sodium cyanide intravenously causes a sudden gasp by action on the carotid sinuses It, however, is likely to produce untoward reactions and therefore is not recommended. In 1936 workers in our laboratory introduced the use of a substance which has proved of interest, first, because it gives a relatively clear end-point and, second, because it permits the measurement of the time of peripheral circulation to the tips of the extremities The solution contains magnesium sulfate 42 Gm , calcium gluconate 16 Gm , sodium chloride 0.9 Gm , and copper sulfate 1 mg per 100 cc.

dilated, but the venous limb may be markedly enlarged, frequently being many times normal size. At room temperature and with freedom from nervous tension the patent arterioles are not in spasm The flow is nevertheless sluggish and there are often prolonged periods of stasis. Extravasations of blood into the surrounding tissues are frequently seen As the phase of spasm appears the arterioles apparently contract, reducing the blood flow. This results in loss of red blood cells from many capillaries as they drain into the venules, and hence the capillaries become invisible. Movement of the blood can then not be seen, the pallor of the skin becomes pronounced and an incision of the skin at that time may produce little or no bleeding. The phase of cyanosis is entered upon; intermittently clumps of cells are admitted, but their color appears to be darker than the average normal. With the release of arteriolar spasm, when the phase of hyperemia supervenes, the capillaries become engorged, the blood flow is suddenly and rapidly restored, and the color of the blood and the skin becomes bright red The picture of Raynaud's syndrome is perhaps the most characteristic observed by capillary microscopy.

When scleroderma develops, with or without Raynaud's syndrome, visualization of the capillaries becomes very difficult They appear to be obscured by a film or cloud, probably due to development of excess collagenous material in the skin. When the flow can be seen it is usually slow and the blood frequently cyanotic.

The long-recognized tendency of blood cells to clump together, forming in some instances a block in a small vessel or moving in a mass, has been labeled "sludging." This has been observed in many patients and a wide variety of conditions, but its significance is not clear. This is especially interesting as it occurs in patients with cryoglobulinemia when the temperature of a distal part is lowered below a critical point for the precipitation of the cryoglobulin—usually 37 C. (98.6 F.).

the left ventricle to the perineum is estimated by subtracting the arm-to-tongue from the arm-to-perineum time The time from the ventricle to the right foot is calculated by subtracting the arm-to-tongue from the arm-to-foot time. Time to other areas is similarly calculated.

Kvale and Allen made exhaustive studies with this substance and this technic, comparing its action with that of various other substances, including sodium cyanide. They concluded that there was an error inherent in the sodium cyanide method and that the values obtained by that method were 3 ± ½ seconds greater than they should be Using Macasol they found the following times in normal subjects under control conditions· arm to tongue, mean 13.50 ± 0.20, arm to perineum, 21.25 ± 0 41; arm to right hand, 23.40 ± 0.43; arm to left hand, 23.65 ± 0.48; arm to right foot, 34.70 ± 0 85; arm to left foot, 34.35 ± 0 85. With chronic occlusive arterial disease the average time required for the blood to flow to the feet was increased However, in many individual cases circulation time has been found to fall within normal limits. We therefore concur in their opinion that tests for the speed of arterial circulation cannot be considered conclusive for the diagnosis of chronic occlusive disease. Collateral circulation may apparently have a rate of flow which distributes blood as rapidly as do the normally functioning major vessels.

The rate of blood flow is definitely increased in patients with hyperthyroidism. In patients with essential hypertension it averages about the same as in normal persons In patients with cardiac decompensation or marked disturbances of the pulmonary circulation the circulation time frequently is definitely prolonged. Hitzig devised a method for differentiating the right and left circuits on a physiologic and dynamic basis, using ether as a volatile substance. He measures the time necessary for the characteristic odor to be perceptible to the investigator or to the patient.

Five minims of ether and 5 minims of normal saline solution are *drawn into a 1 or 2 cc syringe to which a 20 gauge needle has been*

of distilled water * Two cubic centimeters of the solution is used for each test The technic follows.

The patient is supine with the arm at heart level. A tourniquet is applied to the arm, 2 cc. of solution is drawn into a 2 or 3 cc. syringe with a 20 gauge needle, and the needle is inserted in the vein The tourniquet is removed and after three to five seconds the solution is injected as rapidly as possible. The solution produces the sensation of extreme warmth in the tongue or throat, perineum and feet as it reaches these respective portions of the anatomy. The patient is instructed regarding what to expect and is told to report immediately the appearance of the sensation, saying "tongue," "crotch," "hands," "feet." If it reaches one hand first he says "right hand" or "left hand," as the case may be, and the same with the feet When the test is being performed the technician doing the test says "go" and his assistant starts a stop watch The circulation time is recorded as the patient designates the various points at which the sensation is perceived.

It is not certain that the sensation of warmth in the hands or feet indicates that the solution has actually arrived concurrently at those points, but it appears that this reasoning is correct. It is, therefore, possible to indicate the time elapsing between the beginning of the injection and the appearance of a sensation of warmth throughout the portions of the body mentioned, for instance, arm to tongue, arm to right hand, arm to left foot, arm to crotch. Rarely a patient is apparently unable to perceive the sensation, and in such cases the term "blank" is used. Frequently on repetition of the test the patient is able to name clearly the times at which he perceives the sensation.

This study does not permit exact determination of velocity of flow of the blood in the arteries, because there is no positive means by which the time at which the solution leaves the heart can clearly be determined. The time required for the blood to move from the left ventricle to the tongue appears to be about one second. Since it is relatively constant and relatively short we therefore eliminate it from the calculations. The circulation time from

* This solution is known as Macasol.

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Five minims of ether and 5 minims of normal saline solution are drawn into a 1 or 2 cc. syringe to which a 20 gauge needle has been

attached The solution is injected into a large antecubital vein and the ether circulation time is determined as the odor perception end-point. The ether passes through the peripheral venous segments to the right side of the heart and pulmonary arteries into the pulmonary arterial capillaries where it volatilizes into the pulmonary alveoli. It is then exhaled with great rapidity through the air passages to the olfactory organ A solution containing 2 5 Gm of saccharin in 3 cc of water* is then injected in the same manner, and the time required for the solution to pass from the antecubital vein to the tongue is recorded as the saccharin circulation time By subtracting the ether time (the measure of the right heart time) from the saccharin time, the time required for the blood to pass from the pulmonary capillaries to the tongue is determined. This Hitzig calls the saccharin time-ether time difference.

According to Hitzig and others, the right and left heart times are normal in pneumonia, empyema, bronchiectasis, lung abscess, bronchitis, pneumoconiosis and tuberculosis. Mediastinal, pleural and pulmonary malignant tumors, Pick's syndrome, atelectasis, bronchial asthma and numerous other pulmonary conditions are usually associated with normal circulation time. As failure of the right heart develops the ether time becomes prolonged, therefore an ether time within the normal range (eight seconds) is evidence against failure of the right side of the heart

When aqueous sodium fluorescein is administered intravenously according to the method developed by Lange and Wollheim, the interval between the injection of the dye and the appearance of a greenish-yellow glow in the conjunctiva when the patient is [illegible]d under an ultraviolet light in a dark room has been [illegible]ized as the circulation time Sicher and Sheard modified this for use in the study of patients with vascular disease. Their [illegible]nic follows.

Three cubic centimeters of a 20 per cent aqueous solution of sodium [illegible]rescein is found to give the sharpest end-points. The patient is [illegible]d while lying on a dark background in a darkened room The [illegible]tion of 3 cc. of fluorescein into an antecubital vein is given under

* [illegible]ng 2.5 Gm. of soluble saccharin to 3 cc of distilled water. [illegible]ing, then cooled to body temperature before being injected.

an ultraviolet light. A small water-cooled mercury vapor lamp fitted with two thicknesses of Corning heat-resistant red-purple-ultra no 587 glass filter is used as a light source The part to be observed is then illuminated and the time recorded when the end-point is reached The end-point consists in the first definite appearance of a greenish-yellow fluorescent glow of the hitherto dark purple part Timing is done by means of a kymograph

This test, although it indicates that the circulation time is prolonged in cases of arteriosclerosis obliterans and thromboangiitis obliterans, requires special equipment and technic and will not be further elaborated here.

SECRETION OF SWEAT

At times it is of clinical interest to know whether certain areas of the body are capable of sweating or not Various methods and chemical compounds have been used for this purpose In 1935 Roth devised a practical technic based on the fact that in the presence of sweat cobaltous chloride in a saturated alcohol solution, which is normally deep blue, turns to bright pink

With a small brush a little saturated alcohol solution of cobaltous chloride is applied over the parts of the body in which the presence or absence of sweating is to be determined. The solution is either dotted [illegible] skin dries readily [illegible] inet large enough [illegible] ining a series of incandescent light bulbs which maintain a temperature of 130–140 F (54.4–60 C.) is placed over the patient. Wherever sweating occurs the dots and stripes of the solution turn bright pink In places where varying degrees of sweating are observed the transition can be noted with considerable accuracy by change in color of the cobalt Sufficient moisture may be present in the air to change the color of the solution, but never to the deep pink observed in the presence of sweat.

Various drugs may be used to produce sweating Pilocarpine hydrochloride has been administered subcutaneously for this purpose, and Guttman has used Furmethide, a drug with a parasympathomimetic action considered superior to pilocarpine and freer

from side effects. Furmethide is administered by subcutaneous injection of 5 mg, which produces sweating on the face, upper extremities, thorax and abdomen within two to five minutes Sweating is increased after the administration of nicotine in some cases of hemiplegia, herpes zoster, tuberculosis and hyperpituitarism, in most cases of fever and practically all cases of vasomotor disturbances such as Raynaud's disease. It should be noted, however, that increased perspiration alone has little if any diagnostic significance in these conditions. Many patients have conspicuous increase in local sweating of the extremities without evidence of peripheral vascular disease Especially with neurocirculatory asthenia and acrocyanosis, hyperhidrosis of the hands and feet may be so severe as to cause maceration of the skin Drops of sweat may fall at frequent, regular intervals from the tips of the fingers.

Interruption of the sympathetic nervous system produces anhidrosis of the cutaneous area supplied by the severed nerve. It is dramatically demonstrated following bilateral ventrorhizotomy for essential hypertension. On this basis ganglionectomy is performed for marked hyperhidrosis. Many of the patients with frostbite and trench foot observed in army hospitals had as their most disagreeable and persistent complaint copious sweating which rapidly saturated their socks and the linings of their shoes. They frequently also complained of marked paresthesias. Lumbar ganglionectomy was performed on a number of these soldiers The paresthesias were seldom relieved, but the sweating promptly ceased.

Psychogenic factors play an important part in the excretion of sweat. They include anxiety, fear, joy, anger, pain and gastrointestinal cramps. It is not unusual for sweating to accompany fainting As mentioned previously, excessive palmar sweating is common in neurocirculatory asthenia. A decrease in sweating may occur with neurologic disturbances, including multiple sclerosis, syringomyelia, poliomyelitis and tumors of the spinal cord. It has also been noted in individuals exposed to active desert life. For example, it was noted by Wolkin, Goodman and Kelley in soldiers

in active military training in the California desert. First they perspired profusely, following which anhidrosis developed Return to a cooler environment and rest led to speedy recovery.

The cobalt blue test is a useful simple procedure when the examining physician wishes to determine in greater detail the tendency to sweating in a given patient

VENOUS TESTS

It is frequently desirable to determine in detail the status of the venous circulation. Some relatively simple tests to facilitate such an examination will be described.

Venous pressure.—Various simple instruments have been used to determine venous pressure since Hales in 1733 inserted a glass tube in the jugular vein of a mare and measured the pressure by determining the height of the column of blood which rose in the tube. U-shaped manometers have been used with satisfaction Of equipment at present available, perhaps the simplest is that utilized by Cohen. It consists of an upright glass manometer tube, a three-way stopcock and Luer glass syringe with a needle

The patient should rest for at least 15 minutes in the supine position to standardize the procedure The arm is placed so that the antecubital vein to be used is actually 5–6 cm below the fourth interspace at the sternum. (This is hypothetically the point at which the superior and the inferior vena cava enter the right auricle.) A local anesthetic, such as procaine hydrochloride, may be infiltrated beneath the skin over the vein, although I have found it unnecessary

Three per cent sodium citrate solution is used in the syringe to prevent coagulation of the blood. Venipuncture is made in one of the prominent veins at the elbow and a small amount of blood is drawn back into the syringe. The stopcock is then turned and the fluid in the syringe is forced into the manometer tube to a point above the expected venous pressure Next the valve is turned and the fluid allowed to run from the manometer into the vein The point at which the flow stops is taken as the venous pressure

The equipment is essentially the same as the spinal manometer,

except that the manometer has a slightly larger bore. Spinal manometers may be used for this purpose.

According to Rutledge the normal venous pressure using Cohen's instrument varies between 3 and 20 cm. of water. He found considerable variation in the course of the day, but it was difficult to correlate the variation with a degree of activity, eating or other factors of that order He also failed to find a correlation between levels of venous and arterial pressure or between venous pressure, age, height and weight of the subject. Differences in venous pressures of the arms and legs were noted, but it was impossible to predict which would be higher.

In the presence of cardiac failure the venous pressure markedly increases, but in hypertension without cardiac failure an increase is not necessarily present In general the height of the venous pressure parallels the degree of right congestive failure, and the pressure falls as the congestive failure is relieved There is no increase in venous pressure with polycythemia vera, primary varicose veins or occlusive arterial vascular disease. There is a marked increase in venous pressure in a limb in the presence of one or more arteriovenous fistulas

Following thrombosis of major veins, the venous pressure is apt to be increased peripherally from the point of thrombosis. Careful observation for an increase in size or noticeable engorgement of the veins in the neck and arm may give the observer information regarding increased venous pressure. The following simple test is often helpful in making a rough estimate

The patient lies in the supine position. The veins of the hands are usually either very slightly distended or not distended at all If they show marked distention it is often of interest to elevate the hands slowly from the horizontal position. The height at which the veins drain out and become flat is noted. This should not ordinarily be more than 10 cm. above the anterior surface of the heart. Distention above that level probably indicates increased venous pressure Distention of the jugular veins and also the veins of the under surface of the tongue is suggestive,

but not conclusive, evidence of increased venous pressure. These observations must be made with the patient supine.

Venous filling time.—This observation has been used as a rough gauge of arterial insufficiency of the vessels supplying the feet and legs

The test is performed by having the patient, who is supine, elevate the feet and then place them in a dependent position. The length of time necessary for the veins of the dorsum of the foot to fill to normal distention is measured. In the average normal individual this takes 10 seconds or less Frequently in persons with arterial occlusive disease 35 or 40 seconds is required. The assumption is that this is the time required for the blood to come through from the arterial side in sufficient quantity to distend the veins It is necessary, however, to be certain that the blood does not return from above downward through varicose veins which may leak backward. Careful observation will disclose whether or not the blood is coming from the distal portion of the foot

It should be remembered that a vasospastic state, present in some hyper-reactive individuals or produced by marked chilling, may be responsible for a delayed or incomplete venous filling time The test should therefore be made only when the patient is completely relaxed and after he has been in a warm environment for 30 minutes or more

TESTS FOR COMPETENCE OF SAPHENOUS AND COMMUNICATING VEINS AND OCCLUSION OF DEEP VEINS

Numerous tests have been described for determining the competence of the valves in the saphenous and communicating veins and the presence of an important occlusion of the deep venous circulation. A few of the most useful ones will be described

Brodie-Trendelenburg test—This test, first described by Brodie in 1846, is one of the best known

The superficial veins of the leg are drained of blood and collapsed by having the patient assume the supine position and elevate the leg With the fingers, sufficient pressure is made over the upper portion of the saphenous vein to keep its lumen occluded. The patient then stands, and the pressure is released quickly. These maneuvers are repeated, except that the pressure is maintained for 35 seconds the second time

except that the manometer has a slightly larger bore. Spinal manometers may be used for this purpose.

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cm. above the anterior surface of the heart Distention above that level probably indicates increased venous pressure. Distention of the jugular veins and also the veins of the under surface of the tongue is suggestive,

In interpretation of the results, if varices disappear rapidly when the patient walks, the saphenous veins are incompetent, but the valves of the communicating veins are competent. If varices do not disappear on walking, the valves in both the saphenous and the communicating veins are incompetent If varices become more prominent on walking, especially if the patient experiences pain, the deep veins are obstructed and the valves of the communicating veins are incompetent. This last phenomenon is based on the fact that there is incompetence of the communicating veins between the long and the short saphenous system

Ochsner and Mahorner devised a modification of the Perthes test which is, in fact, three separate Perthes tests (1) with the tourniquet around the upper part of the thigh; (2) with the tourniquet around the middle of the thigh, and (3) with the tourniquet just below the knee. This procedure helps in determining the exact location of incompetent communicating veins between the superficial and the deep system. For example, if with the tourniquet applied just above the knee varices below the knee disappear after walking, this is interpreted to mean that the communicating veins below the point of the tourniquet have competent valves If with the tourniquet around the middle or upper part of the thigh the varices in this area do not collapse after walking, the communicating veins in this area of the thigh are probably not competent

Pratt's test.—Pratt described a test for incompetent communicating branches which has proved very useful in our experience

With the patient lying down, the leg to be tested is elevated and with light massage the veins are emptied. The tourniquet is placed high enough on the thigh to close off the saphenous vein and an Ace bandage is applied from the toes to the tourniquet. The patient then stands up and the Ace bandage is slowly unwound from above down. With the tourniquet above preventing a reflux of femoral blood through the saphenous valve and with the Ace bandage below compressing the remainder of the saphenous vein, a bulge or "blowout" indicates an incompetent communicating branch vein Such an area is marked with an

The results of the test are recorded as follows. (1) The result is termed "positive" if the varices fill rapidly when the pressure is released quickly with the patient standing and fill slowly when the pressure is maintained and are not distended completely at the end of 35 seconds (2) It is "negative" if the varices fill slowly from below when the pressure is maintained and are completely filled at the end of 35 seconds and fill no more rapidly when the pressure is immediately released. (3) The result is called "double positive" if the varices fill rapidly after immediate removal of the pressure of the fingers and also when the pressure is maintained (4) It is called "nil" if the varices fill only slowly when the pressure of the fingers is removed quickly and also when the pressure is maintained. The following interpretations may be made. "Positive" indicates incompetence of the valves of the long saphenous vein but competence of the valves of the communicating veins "Negative" means competence of the valves of the long saphenous vein but incompetence of the valves of the communicating veins. "Double positive" may mean incompetence of the valves of both the long saphenous and the communicating veins Frequently it means incompetence of the communicating veins between the greater and the lesser saphenous system and incompetence of both systems. This can be ascertained by performing the test after occluding both the long and the short saphenous vein at the proximal ends. "Nil" means functional competence of the valves of both the long saphenous and the communicating veins. In some cases of very early incompetence, nil may be obtained.

Perthes' test.—This test is based on the fact that the flow in the venous system of the leg depends in large part on muscular action, since the flow is normally from the superficial to the deep system at numerous levels.

A tourniquet is applied to the thigh tightly enough to compress the long saphenous vein and to prevent the flow of blood in the superficial system past this constriction. The patient then walks briskly and the prominence of the varicose veins is noted

In interpretation of the results, if varices disappear rapidly when the patient walks, the saphenous veins are incompetent, but the valves of the communicating veins are competent If varices do not disappear on walking, the valves in both the saphenous and the communicating veins are incompetent If varices become more prominent on walking, especially if the patient experiences pain the deep veins are obstructed and the valves of the communicating veins are incompetent. This last phenomenon is based on the fact that there is incompetence of the communicating veins between the long and the short saphenous system

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indelible pencil as the point where a secondary ligation will be required. In an extremity showing many such blowouts, a second Ace bandage is applied from above down As the first Ace bandage is slowly removed, a blowout appearing between the two bandages is a new one and must be marked and resected

Pratt commented "While in most instances, there are only one or two such 'blowouts,' one sometimes finds four or five. Failure to remove such 'blowouts' results in recurrences. From a practical standpoint, while doing this test one has also tested the patency of the deep femoral veins because if there were a thrombosis of the deep veins, the tourniquet would prevent a return flow through the saphenous tree, and there would be no venous return from the limb with resultant severe pain and swelling of the calf."

In reports of the status of the circulation as determined by the foregoing tests, it is important that an exact description of the vein and whether it is competent or not be entered Confusion in the recording of the results of these tests is increased by the use of such terms as "positive" or "negative" alone One should state whether the superficial or deep systems are patent and whether the valves are competent. One should also note whether the communicating veins are functioning and, if they are not functioning satisfactorily, where blowouts are found and where communicating veins must be ligated in the event any surgical procedure is undertaken.

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indelible pencil as the point where a secondary ligation will be required. In an extremity showing many such blowouts, a second Ace bandage is applied from above down. As the first Ace bandage is slowly removed, a blowout appearing between the two bandages is a new one and must be marked and resected

Pratt commented "While in most instances, there are only one or two such 'blowouts,' one sometimes finds four or five Failure to remove such 'blowouts' results in recurrences. From a practical standpoint, while doing this test one has also tested the patency of the deep femoral veins because if there were a thrombosis of the deep veins, the tourniquet would prevent a return flow through the saphenous tree, and there would be no venous return from the limb with resultant severe pain and swelling of the calf"

In reports of the status of the circulation as determined by the foregoing tests, it is important that an exact description of the vein and whether it is competent or not be entered Confusion in the recording of the results of these tests is increased by the use of such terms as "positive" or "negative" alone. One should state whether the superficial or deep systems are patent and whether the valves are competent One should also note whether the communicating veins are functioning and, if they are not functioning satisfactorily, where blowouts are found and where communicating veins must be ligated in the event any surgical procedure is undertaken

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CHAPTER III Arteriosclerosis Obliterans—Atherosclerosis

THE IMPORTANCE of arteriosclerosis obliterans cannot be overestimated in terms of seriousness to millions of individuals or in the determination of world history The position may be taken and rather well defended that most if not all evidences of senility are secondary to the primary mechanism of arteriosclerosis; that the resulting signs and symptoms are merely accidental, depending on the portion of the arterial tree which is sufficiently damaged to prevent adequate blood supply, and certain organs thereby thrown into a state of imbalance developing not only local manifestations but far-reaching general reactions of great importance. Just as Zinsser was able to present facts demonstrating the great importance of infection in world history, one might well marshal strong evidence to prove that nations have fallen and peace conferences have failed because of the presence of cerebral arteriosclerosis in the leaders. Countless examples might be cited of warped management and inhibited progress in many institutions as a result of this factor in more than one cortex around the directors' table Annual examinations from this point of view might well be considered for individuals holding important civil, military and industrial positions.

Specific examples of general reactions which may occur in an individual as a result of localized arteriosclerosis are the involvement of the arteries of the pancreas with the development of dia-

betes mellitus and all of its complications, and that of the arterial disease, uremia, hypertension and many other related conditions.

Local reactions may be cited in terms of arteriosclerosis of ves tree of the kidney with the development of secondary kidney sels of the extremities. If a small artery supplying a group of muscle fibers becomes blocked, intermittent claudication may develop, with pain sharply localized in a small mass of muscle which becomes ischemic owing to the circulatory deficit developing with exercise. This syndrome may be of short duration if collateral vessels take over the burden, or it may become widespread secondary to the propagation of a thrombus and blocking of larger branches of the arterial tree. An example of local damage is the gangrene frequently found in the tip of a digit caused by blocking of an artery or arteries supplying that digit. If one considers the possibilities for similar occurrences in any of the organs and tissues of the body, the kaleidoscopic variations of pathologic change secondary to arteriosclerosis obliterans become apparent. If one includes the coronary, cerebral, mesenteric and other arterial groups, it becomes clear that many deaths and diseases now classified under the organ involved should be classified as arteriosclerosis, with the organ relegated to a secondary position. This places arteriosclerosis obliterans foremost, from the point of view both of incidence of disease and as a cause of death.

Some conception of the incidence may be obtained from the following figures. It has been estimated that there are at least 25,000,000 persons more than 50 years of age in the United States. Of these, 60 per cent, or 15,000,000, will die of some cardiovascular-renal syndrome, in contrast to 9 per cent who will die of cancer. A large but undetermined portion of the 60 per cent will die as a result of degenerative changes of the arteries, with the secondary changes already mentioned. Arteriosclerosis, therefore —the number one disease problem in this country—deserves much more serious consideration and more widespread investigation

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than it has hitherto received either from the medical profession or from the lay public

General Considerations and Nomenclature

The term arteriosclerosis has come to have a broad meaning which includes several conditions that differ in their pathogenesis and their prognosis.

I Of these, the most important clinically is that now known as *atherosclerosis* or *atheromatosis* The typical lesions are patches of cholesterol, cholesterol esters, phospholipids, fatty acids and neutral fats which form in the intimal layer of the arteries and produce thickening, impingement into the lumen and finally narrowing which encourages local blood clotting and occlusion of the vessels Most cases classified clinically as arteriosclerosis obliterans are of this type It develops in the natural course of the lives of all individuals but at vastly different rates.

II. The second type of lesion to be included under the broad term of arteriosclerosis is the medial calcification known as *Mönckeberg's sclerosis.* The lesion is characterized by a diffuse distribution of calcium confined largely to the medial layers of the arteries It may be so widespread and severe as to produce the so-called "pipestem" appearance on x-ray films. It may occur under several conditions. (1) in the course of aging without other known pathologic process, (2) idiopathically in the early years of life; (3) associated with the osteitis fibrosa of Paget; (4) associated with the excessive destruction of the bones in chronic osteomyelitis; (5) as a result of excessive vitamin D administration; (6) with hyperparathyroidism.

This is not to be confused with atherosclerosis. It rarely causes obliteration of vessels by direct impingement. Barr has suggested that at times it may contribute to the development of atherosclerotic plaques by interfering with normal absorption and *transmission* of the lipids through the arterial wall; this concept, however, is

hypothetical. The two conditions must now be considered distinct entities.

III. The third condition commonly classified under arteriosclerosis but differing from the types already discussed is *arteriolosclerosis.* It may occur coincidentally with the others. The lesion of the arterioles develops in the course of hypertensive and renal diseases, and etiology, natural history and prognosis differ from either atherosclerosis or Mönckeberg's medial sclerosis

IV. Diabetes mellitus is notoriously associated with an increase in arterial lesions. *Atheromatous plaques are more common than* normal and, in addition, the proliferative retinitis and intercapillary glomerulosclerosis of Kimmelstiehl-Wilson are seen. These do not appear to be developed by identical mechanisms

V. Premature atherosclerosis does develop with the hypercholesteremia of nephrosis, myxedema, xanthomatosis and with familial hypercholesteremia

An attempt will be made to use the correct term throughout this chapter, although it is recognized that there may be definite coincidental overlapping of processes in some patients.

For a more comprehensive summary of these and other important aspects of this problem, the reader is referred to the work of Dr. David Barr, who kindly permitted me to review his lecture on The Pathogenesis of Atherosclerosis prior to publication *

Pathogenesis

Age —In man it is commonly observed that there is a roughly *parallel incidence of increasing atherosclerosis* with *increasing* age. This is to be expected since normally the intima increases in thickness 30 times from birth to age 50 and three times from age 16 to 50. This is much more pronounced in the systemic (*major*) *circulation than in the pulmonary* (minor) circuit. There are, however, many young persons below the age of

* *Annual Lecture, Cleveland Academy of Medicine, May 18, 1951.*

40 with marked evidence of sclerotic changes and, in contrast, many individuals of 65 or 70 who, even at postmortem examination, reveal surprisingly few signs of sclerosis. During World War II it was demonstrated that it is not rare for atherosclerotic changes to be responsible for death from coronary thrombosis in young men, 800 or more cases occurring in the armed forces of the United States in men under 40. While acting as Consultant in Medicine and moving from one Army hospital to another for several years, I saw each month from one to four cases of coronary thrombosis in men under 40.

It is not generally realized by the medical profession that such atherosclerosis can be responsible for death in young children Cases have been reported in children from 10 to 15 years of age. The youngest case, however, with which we are familiar is one cited by Stryker in which such a lesion of a coronary artery caused the death of an infant 3 months old. The illness had lasted only three days and was thought to be influenzal pneumonia. At autopsy one coronary artery showed calcification of the media and fibroblastic proliferation of the intima with complete occlusion of the lumen except for small foci of canalization Other coronary arteries showed less pronounced processes. Small areas of recent infarction were present in the myocardium. Arterial changes similar to those in the coronary arteries were found in pulmonary and splenic arteries. In other infants aged 2 and 6 months focal calcification of the media of the main coronary artery has been found. The etiology in these cases is not understood, but the occurrence of the phenomenon in extremely young children is mentioned at this point so that it may be kept in mind

It is noteworthy that, despite the incidence of calcification in the coronary arteries of young individuals, calcification is rarely encountered in the lower extremities as a disabling factor in individuals under age 30. Soft tissue x-rays may reveal calcified arteries in young men without symptoms. These are usually of the Monckeberg medial sclerosis type.

Aside from the exceptions just cited, certain progressive chronologic arterial changes proceeding at varying rates may be anticipated in older individuals. One is the gradual diffuse distention of the vessels due to progressive deterioration of the elastic tissue in the walls. The stretching process occurs in the longitudinal as well as the circular direction. From early youth the internal elastic membrane tends to split, and this process becomes more marked as the years pass. Arteries are under longitudinal tension early in life. On the average, by age 40 stretching has taken place to relieve this tension, and from then on overstretching occurs, resulting in tortuosity. The deterioration of the elastic tissue with age is similar to processes which take place in all colloidal substances. This change is associated with the progressive accumulation of finely divided calcareous material in the media that begins early in life and becomes more marked with senescence. Winternitz and his co-workers have published studies which suggest that vascularity of the walls of sclerotic arteries is frequently increased and may be associated with minute hemorrhages from the vasa vasorum. They believe that frequently the hemorrhages become calcified and by rupture through the intima may pave the way for the development of thrombosis The hemorrhages probably are late manifestations and are not concerned with the original development of arteriosclerotic lesions The absence of an exact parallel between age and the development of sclerosis implies that age per se is not the cause of these changes, but rather that the changes are secondary to one or many factors affecting the life of an individual through the years. The more significant of these possibilities will be discussed.

Race and climate.—Studies of the effects of race and climate on the development of arteriosclerosis have been unsatisfactory and inconclusive. Various workers who have had an opportunity to observe Oriental peoples have reported that incidence of arteriosclerosis among the Chinese is lower than that among Occidentals of comparable age groups The point is not definitely established.

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William T. Foley, who has studied clinical and pathologic material in China, believes that his experience confirms this general impression Whether the difference in incidence is due to race, climate or diet remains to be established, but it appears possible that the low fat, low cholesterol diet may be an important factor.

Sex.—The relationship of sex and the development of arteriosclerosis has considerable interest The general impression has been that men develop arteriosclerosis and die of it at an earlier

TABLE 1.—INCIDENCE OF ARTERIAL IMPAIRMENT ACCORDING TO SEX AND AGE

(Physical Findings)

	MEN	WOMEN
40–49 yr.	27%	8%
50–59 yr	55	26
60 yr and over	77	56
Total	46%	20%

TABLE 2.—INCIDENCE OF CALCIFICATION ACCORDING TO SEVERITY*

(X-Ray Evidence)

	MEN	WOMEN
Total	305	231
No. with calcification	135 (44%)	42 (18%)
No with 3 + or 4 + calcification	41 (30%)	3 (12% of those with calcification)

* According to severity of involvement rated from 1+ to 4+.

age than do women It has been generally assumed that this is in part due to the fact that women lead more sheltered lives than do men. Therefore, Lake, Pratt and I studied 536 men and women who had been working at similar occupations—sitting, standing, walking or climbing—in a large department store for a minimum of 10 years (average, 17 years). This study revealed a marked discrepancy between the sexes in the tendency to the development of arteriosclerosis. The subjects were studied for x-ray evidence of calcification and by oscillometric readings and other tests for arteriosclerosis. Tables 1 and 2 illustrate the difference between the sexes.

Animal experiments carried on during the same period by Ludden, Bruger and Wright demonstrated that unprotected male and female rabbits developed atherosclerosis as is usual after prolonged administration of cholesterol. In female rabbits fed cholesterol, the development of hypercholesteremia was inhibited and the deposition of cholesterol in the aorta to produce atherosclerosis was prevented by the administration of testosterone propionate or estradiol dipropionate. In male rabbits fed cholesterol the same steroids exerted little or no such protective action Thus this effect of the steroids varies with the sexes, differing from the inhibiting effects of iodine and other substances on cholesterol deposit in the arteries. The androgen and estrogen were equally effective, suggesting that both steroids produce a common metabolic effect through some action which takes place in the female but not in the male animal. Later work demonstrated that if the females were castrated some factor of protection was lost so that the administration of testosterone propionate or estradiol dipropionate no longer protected against the development of cholesterol atherosclerosis in the aorta following the administration of the same doses of cholesterol.

Although it is recognized that there is risk in making direct comparisons between animal atherosclerosis and atherosclerosis in man, the fact that both of these studies point to a similar protective mechanism in the normal female certainly justifies much more work and thought on the possibility of a hormonal substance protecting the female against atherosclerosis

Hard work, exercise.—Exercise and hard work have long been thought to be associated with the development of arteriosclerosis, based on the concept that long-continued trauma to the walls of the vessels has an important etiologic role In an effort to clarify the problem, Lake, Pratt and Wright divided the aforementioned group of department store workers according to the physical demands of their occupation—sitting, walking, standing and stair-

climbing. It was found that stair-climbing tended to produce a significant incidence of arteriosclerosis in young men approximately one decade earlier than did standing, sitting or walking Above the age of 50 there were no significant differences in the incidence of arterial disease in any of these classifications.

Nutrition —Diet is undoubtedly an important factor in the maintenance of health and the achievement of longevity. It is possible that nutrition influences the development of atherosclerosis by several means· (1) a quantitative deviation from the optimal diet that represents a deficient or excess intake of any of the necessary constituents such as vitamins, proteins, fats or minerals, (2) changes in the relation of one foodstuff to another, and (3) abnormal reactions to the optimal nutritional intake such as may occur with metabolic dyscrasias, gastrointestinal disease and other pathologic conditions

There is no evidence, however, that chronic over- or undernutrition of a purely caloric nature has any influence on the development of atherosclerosis in animals Unbalanced diets fed to animals have led to changes similar to atherosclerosis in man; for example, in rabbits fed diets of meat, eggs and milk or cholesterol, atherosclerosis developed. Chickens develop atherosclerosis under similar conditions, and atherosclerosis has been produced in dogs fed a high cholesterol diet, but only when hypothyroidism has been induced

There are definite data on a relation of excess vitamin D intake and development of atherosclerosis. There does not appear to have been a difference in incidence in individuals who suffered severe malnutrition during World War I and individuals who were obese during the corresponding years Although there is a general impression that the obese are more susceptible to atherosclerosis insufficient evidence is available for proof. Nevertheless, evidence has been advanced that mortality from circulatory diseases decreased in Norway during the Nazi occupation in World War II

The rate rose rapidly on resumption of the normal diet. This should be studied further.

Because of the frequent observation that hypertension and arteriosclerosis are rare in China, where protein-low or protein-free diets are the rule, some workers have held that an abnormal portion of high protein foods may increase the incidence of arteriosclerosis, but the fact that Eskimos living on an animal tissue diet do not show an increased incidence of cardiovascular-renal diseases throws doubt on this hypothesis. More accurate, statistically valid studies on the incidence of arteriosclerosis in the Orient should be prepared.

There is some evidence that a disturbance of lipid metabolism may be an important factor in the development of atherosclerosis in human beings Atheromas do contain a considerable quantity of lipoid material. In human beings, disturbances of lipid metabolism manifested by lipemia are frequently complicated by severe atherosclerosis. It is not uncommon for patients with xanthoma tuberosum with severe lipemia to have pronounced atherosclerosis. Severe lipemia of unexplained etiology is frequently complicated by premature arteriosclerosis obliterans or coronary sclerosis. In myxedema, lipemia is common and the incidence of premature atherosclerosis is high The same developments were observed in diabetics before the insulin era, when they were apt to be on a high fat diet, to which the premature atherosclerosis was attributed. Recently, however, premature atherosclerosis has been recognized in diabetics on the insulin high carbohydrate régime, so the problem requires further consideration

Barker showed that the mean values for plasma cholesterol and cholesterol esters, phospholipids, fatty acids and total lipids were definitely higher in 73 patients with arteriosclerosis obliterans than in 200 normal individuals. This was particularly true in patients between 40 and 60 and in those with premature arteriosclerosis obliterans. There is increasing interest regarding the role of the lipids in the production of atherosclerosis.

Goffman and his co-workers have compiled evidence which suggests that there is a relation between a marked increase of the large cholesterol molecules of the order of S_f 10–20 in the blood and the development of atherosclerosis in man

It has been found that phospholipids act as a stabilizing influence on the lipids in the serum. The ratio of cholesterol to phospholipids may be very important. The higher the value for cholesterol, the greater the tendency to precipitate lipid substances in the arterial wall

Neither cholesterol nor phospholipids exist in a free state in the plasma. They are combined with proteins and are in proportions of 25 per cent alpha-lipoproteins and 75 per cent beta-lipoproteins Barr and his co-workers have observed that in most patients with coronary infarction and atherosclerosis obliterans of the legs with occlusion the alpha-lipoprotein value is low while that for beta-lipoprotein is elevated. This suggests a high cholesterol-phospholipid ratio and may help set the stage for the development of atherosclerotic deposits. It is very possible that Goffman's large molecules of cholesterol are in reality a fraction of beta-lipoproteins. There now seems to be little doubt that patients in whom atherosclerosis develops are likely to exhibit abnormalities in the distribution of lipoproteins.

The ingestion of alcohol was formerly considered a factor. However, Ruffer performed autopsies on over 800 Mohammedan pilgrims and found atherosclerosis to be as common as in Europeans—significant because these pilgrims never admit taking alcohol. Physiologic studies also show no increased incidence in alcoholics as against nonalcoholics. In fact, some workers believe that alcohol may retard the development of atherosclerosis because it is a cholesterol solvent and hence tends to prevent precipitation of cholesterol. The studies of Lake, Pratt and Wright, previously referred to, did not disclose any effect whatever from the use of alcohol (Table 3).

TABLE 3.—INCIDENCE OF ARTERIOSCLEROSIS IN PATIENTS WHO USED ALCOHOL AND THOSE WHO DID NOT

	Men		Women	
	Alcohol	No Alcohol	Alcohol	No Alcohol
% with pathologic changes	46 3	45 7	19 5	20 1
% without pathologic changes	53.7	54 3	80 5	79.9

The same observations have been made regarding the use of tobacco. The figures are not dissimilar to those cited for alcohol (Table 3) and show no statistical evidence that the use of tobacco is related to the development of atherosclerosis. It will be pointed out later, however, that tobacco is interdicted when atherosclerosis obliterans is associated with occlusion impairing the circulation. This is because it has a vasoconstrictor effect on the small collateral vessels which must be encouraged by all means available to dilate in order to take over the work of the larger occluded vessels.

Infections, acute and chronic.—In spite of exhaustive surveys and experimental work there is little evidence that infection plays an important part in the pathogenesis of atherosclerosis. Following typhoid fever, deposits of lipid in streaks and patches are occasionally found MacCallum observed no special tendency to the development of atherosclerosis. in tuberculosis, rheumatism, arthritis, Streptococcus viridans infection and glomerulonephritis.

Diabetes.—With the passage of time atherosclerosis develops in most diabetics to a greater degree than it does in normal individuals. Few juvenile diabetics have survived 25 years without evidence of such vascular changes. This does not appear to be related directly to the degree of control of the sugar values, since very mild diabetics may show striking changes whereas notoriously severe diabetics who "steal" extra food and sweets have in several instances escaped vascular damage to a remarkable degree. This does not indicate that the physician should not attempt to achieve an essentially normal chemistry. It may indicate that the lipid metabolism is more important. Signs of vascular damage include

x-ray evidence of calcification of the vessels, although it should be recognized that this does not indicate the degree of intimal change or narrowing of the vascular lumen Changes in the retinal vessels with increased light reflexes and exudates are characteristic but not specific for diabetes mellitus The development of albuminuria with or without hypertension must suggest the Kimmelstiehl-Wilson syndrome or capillary glomerulosclerosis which frequently occurs in mild diabetics

Heredity.—Although evidence has been advanced to show a marked influence of heredity in the production of hypertension and therefore, by inference, of atherosclerosis, the direct evidence applicable to sclerosis is inconclusive It does appear, however, that in certain families the symptoms and pathologic changes of peripheral atherosclerosis appear earlier than in others. In applying such observations one must consider, however, the extreme difficulty of comparing the total environment—type of work, worry and strain of life, dietary habits and other factors—as well as age of such family groups with those of controls in order to make a just evaluation of the role of heredity

Lead and manganese are believed capable of producing arteriosclerosis, but the type and their role is unsettled.

Pathology

In the study of the pathology of arteriosclerosis, lesions in various stages of development are found in the same process. The atheromatous type of plaque similar to that seen in the walls of the aorta may be found in other larger arteries developing as small, round, grayish or bluish spots which begin to project into the lumen through the intima. These gradually fuse into irregular large plaques projecting farther into the lumen (Fig 23). The development of fibrous tissue makes many of the plaques milky white, while fatty parts break down to become mushy. At this point, either of two processes may take place. The

lesion is sealed by the formation of a calcareous plate, or the softening material breaks down to produce a ragged ulcerating defect at the bottom of which necrotic material may remain Thrombi may then form and cover the ulcer.

Arteries to different organs show variations in the manner of development of atherosclerosis. Our interest in this discussion will be focused in the vessels of the extremities. The aforemen-



Fig. 23.—Arteriosclerosis obliterans ... ed ; Philadelphia F. A Davis Company, 1940])

tioned splitting of the intima is excessive, in advanced stages resulting in marked thickening of the layer because of secondary development of fibrous tissue and the accumulation of cholesterol and lipids The thickening is irregular and leads to eccentric location of the lumen. The degeneration and necrosis involve the intima and media with the deposit of cholesterol crystals. The fibrosis involves the media and adventitia The arteries then become calcified by the development of a circular solid deposit of calcareous material at the more or less obliterated dividing line between the intima and media (Fig. 24). The occlusion—the final stage—is usually due to thrombosis The process in diabetic cases is essentially similar to that described here



Fig. 24 —Arteriosclerosis obliterans Peripheral artery showing thickening of intima and almost complete obliteration of lumen, due to proliferation of endothelium and connective tissue of intermediary layer Degeneration and calcification have taken place in intermediary and muscularis layers, forming a crescent. Elastic laminae are not clearly seen



FIG 25 —Arteriosclerosis obliterans Peripheral artery showing some intimal thickening, though not as much as in Figure 24 Elastic laminae are clearly seen, being obliterated only where degeneration of a large area has taken place Degenerative and calcific changes are most pronounced in the media, suggesting Monckeberg s sclerosis



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In the arteries of the extremities the distinctive type of arteriosclerotic process described by Mönckeberg (1903) is sometimes seen. In this we find *necrosis and calcification* of the media which are not necessarily associated with an intimal lesion, and the process differs thus from atheroma. In advanced cases the arteries may be converted into solid tubes. The deposits may be platelike, circular or tubular or may coalesce to form a tube. This type of sclerosis is relatively common in the extremities Such extremities in which the major vessels show tubular calcification from the iliac vessels down to and including the dorsalis pedis artery may not be gangrenous, the arteries being patent and pulsatile throughout. I have followed a number of individuals who 10–15 years ago showed striking x-ray evidence of this type of sclerosis and who have had no occlusion (Fig 27).

Although it has been generally assumed that these so-called pipestem arteries show a higher incidence of occlusion and at an earlier age than do arteries without pipestemming, in the light of longterm observations it is possible that our previous concepts are in error. The following case is an example.

A surgeon about 12 years ago was found to have pronounced calcification of the vessels of the lower extremities, demonstrated by x-rays. At that time he was carrying without difficulty a heavy surgical schedule in a large hospital The armed services at first rejected him when he volunteered during the recent war, but later accepted him. Throughout the war he carried exceedingly heavy surgical duties which required standing for many hours each day, again without difficulty. He returned to civilian life with no evidence whatever of symptoms related to vascular insufficiency. We no longer give a poor prognosis on the basis of similar x-ray findings

The work of Winternitz on the effect of hemorrhages in the vasa vasorum has been briefly discussed As mentioned, hemorrhages may occur and eventually result in arteriosclerotic plaques, but it is probable that these are rather late effects. The etiology of these hemorrhages deserves discussion. It is possible in some

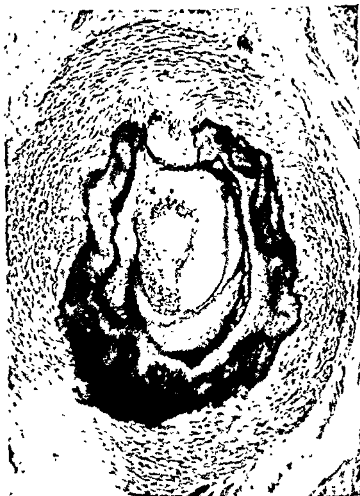


FIG. 26.—Arteriosclerosis obliterans Intima and intermediary layers have been destroyed and replaced by calcification Musculatis is relatively intact

instances that they are due to dietary deficiency, especially of vitamin C, to hemorrhagic diatheses of various types or to increased capillary fragility due to such causes as chemical poisoning and parasitic invasion. They may also be secondary to infectious toxins and to other little understood factors.

The final step in the production of occlusion of an atheromatous vessel is usually a thrombus. It is not understood why thrombi occur at some sites where there is a minimal lesion and do not occur at other sites where the lesion is much more extensive. Many factors, such as an excess of thrombokinase* at the particular point or a change from fibrinogen into sticky insoluble fibrin, may play a role. The organization of a thrombus within the vessel is characterized by disintegration and digestion of the blood elements, accompanied by growth into the clot of capillaries, fibroblasts and many mononuclear phagocytes The process extends until dilated sinusoids connected with tenuous branches canalize the clot which in turn calcifies in other areas This may result in a bizarre formation of vascular channels incorporated in the main lumen of the involved vessel. These channels are often primarily extensions of the vasa vasorum of the vessel wall.

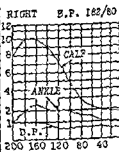
Thrombus formation may be initiated at times by exudative processes Leary has advanced what is known as the foam cell theory. According to this, phagocytic cells of the liver (Kupffer cells) and the adrenals engulf esterified cholesterols, thus becoming foam cells which send migrants through the vascular system finally to invade the intima of some artery. This invasion starts the process of atherosclerosis according to Leary

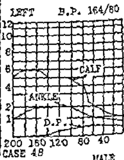
It now appears likely that there is a constant absorption of cholesterol and other lipids through the intima of the arteries and that under certain conditions these substances are laid down to form atheromatous plaques

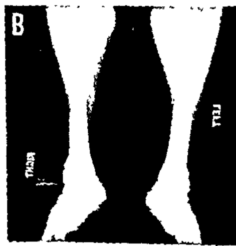
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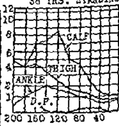
←Fig 27—*A*, striking x-ray evidence of calcification of vessels of lower extremities, with oscillometric values that are normal or better, especially on the right *B*, much less calcification than in *A*, with reduced oscillometric values

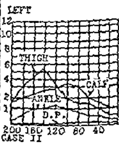

A


RIGHT B.P. 182/80
CALF
ANKLE
D.P.
200 160 120 80 40


LEFT B.P. 164/80
CALF
ANKLE
D.P.
200 160 120 80 40
CASE 48


B


MALE
RIGHT 64 YRS. OLD
38 YRS. STANDING
CALF
THIGH
ANKLE
D.P.
200 160 120 80 40


LEFT
THIGH
CALF
ANKLE
D.P.
200 160 120 80 40
CASE II

instances that they are due to dietary deficiency, especially of vitamin C, to hemorrhagic diatheses of various types or to increased capillary fragility due to such causes as chemical poisoning and parasitic invasion. They may also be secondary to *infectious toxins* and to other little understood factors

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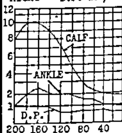
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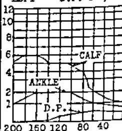
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* Thromboplastin.

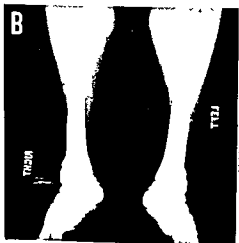
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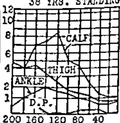


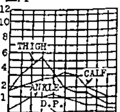


CASE 48



MALE
RIGHT 64 YRS. OLD
38 YRS. STANDING





200 160 120 80 40
CASE II

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The dominant picture in arteriolar changes is intimal hyalinization. This is increasingly widespread and severe with advancing hypertension and nephritis Medial hypertrophy and degeneration

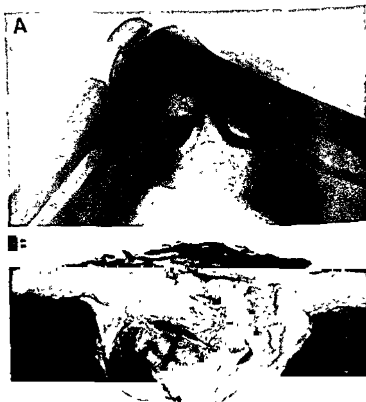


FIG 28—*A*, true arteriosclerotic aneurysm of popliteal artery Aneurysmal repair was advised, but refused Six months later amputation was necessary *B*, large ruptured aneurysm and mass of clot from same patient.

resemble changes following distention of any hollow muscular structure. Medial degeneration may be primary in some instances, but medial hypertrophy is probably secondary to stress and strain, *being present more frequently in hypertensives than in non-*

hypertensives Intimal proliferation in the form of endothelial hyperplasia with increase in elastic tissue and secondary degenerative changes may be classified as endarteritis obliterans rather than arteriolosclerosis obliterans.

True and false aneurysms of the peripheral arteries are extremely common late effects of arteriosclerosis and are discussed in Chapter XI In arteriosclerosis they occur as dilating saccular or dissecting aneurysms. Many rupture to produce false aneurysms, which may occur anywhere, but especially where stress and strain are greatest The popliteal space is a common site (Fig. 28)

Signs and Symptoms in the Extremities

Arteriosclerosis should be considered a generalized disease potentially occurring in any or all of the arteries of the body simultaneously Actually, the process is more likely to be advanced in *some segments of the arterial tree than in others This discussion is* confined largely to the effects of the process in the arteries of the extremities, although it should be clearly understood that occlusion of any artery of the body interferes with the nutrition of the tissues supplied by that artery and in so doing initiates signs and symptoms which vary according to the type of tissue which becomes ischemic Physicians have been wont to think in terms of the organ affected instead of the fundamental condition which has interfered with the circulation and hence the functions of the organ For example, as previously mentioned, in older people diabetes mellitus is often secondary to arteriosclerosis obliterans of the arteries of the pancreas Not infrequently arteriosclerosis of the vessels of the kidneys is responsible for the development of renal symptomatology The correct diagnosis in such cases should be arteriosclerosis with secondary diabetes mellitus or nephrosclerosis There are many similar examples

In the extremities, certain signs and symptoms are important.

1 Pain This is the symptom which most frequently bring the patient with arteriosclerosis obliterans of the lower *extremities to*

the doctor. The types of pain vary widely, the two most common being the pain of intermittent claudication and pain at rest.

a) The syndrome of intermittent claudication is typified by extreme fatigue, tightness or cramplike pains in the calves of the legs or the muscles of the thighs which develop when the patient walks a limited distance and which often force him to a dead stop After a few minutes' rest the patient can proceed for about the same distance before similar symptoms once more force him to stop. Rarely in laborers we have seen this phenomenon in the muscles of the arms The severity of claudication is sometimes increased by cold weather It is also made more severe by walking rapidly, or up hill, even the most modest grade accentuating the symptoms.

As the disease progresses with blockage of the larger vessels the areas of claudication pain ascend the leg until ultimately the thigh is involved and the vessels of that area are nonpulsating and occluded. It should be remembered, however, that in some patients the major vascular trunks may be patent down to and including the dorsalis pedis artery, while some branches supplying important groups of muscles in the thighs or calves are occluded As a result, intermittent claudication may occur from ischemia in a group of muscles high in the leg while the dorsalis pedis is patent and pulsating.

The pain of intermittent claudication must be differentiated from rheumatic or arthritic pains In addition to tests for vascular or joint damage we have found it helpful to determine whether the patient has to sit down to obtain relief. The patient with joint disturbances usually has to take the weight off the affected joints, whereas pain due to ischemia (true claudication) can be relieved merely by interrupting active exercise of the muscles. The logical explanation for this, in the light of our present understanding of the cause of claudication pain, seems to be that some chemical substance accumulates in the muscles during work when the blood supply is deficient. When no further work is demanded of the

muscles the diminished blood supply proves adequate to remove the metabolic products and supply sufficient nutrition. The syndrome is readily reproduced by the application of a tourniquet bound tightly around an extremity to occlude the arterial blood supply, following which exercise is taken

Roth has shown that the lactic acid of the venous blood of an extremity involved by occlusive vascular disease *increases* sharply after exercise, but this is *not consistently* parallel to the intensity of pain.

b) Rest pain Pain that develops during rest occurs characteristically when the patient is lying in bed The pain is typically cramplike There is some debate about the cause, although I believe it is associated with local ischemia which results from stagnation of the blood, with secondary utilization of oxygen and the accumulation of toxic waste products in the tissues An occasional patient has severe rest pains in the feet with no demonstrable lesions aside from atrophy of the skin and muscles. I have seen a few cases in which pain was so severe that despite all present-day methods of treatment amputation was required. In general, however, the pain of arteriosclerosis is apt to be subacute, of rather a dull aching nature which frequently accompanies the development of ulcers.

The patient's bed must be considered carefully Many beds sag in the middle so that the feet, or at least the toes, are higher than the pelvis or even the heart level Since the blood must then flow up hill through defective pipelines, this may greatly aggravate the ischemia over a period of hours

2. Temperature and other sensory changes A common complaint of patients with arteriosclerosis obliterans is that their hands or feet are cold and that it is difficult to get them sufficiently warm to be comfortable Studies of the surface temperature demonstrate this coolness even in the many patients who do not seem conscious of cold extremities. Lowered temperature almost inevitably accompanies arterial occlusion unless the collateral vessels have taken

over the full burden of the circulation. Normal skin temperature in a room of average temperature (20–25 C; 68–74 F.) averages 29 5–33.9 C (85–93 F.), but many extremities with advanced arteriosclerosis persistently maintain temperatures as low as the room temperature Cold feet or hands, however, may be due to vasospasm without occlusive disease.

Occasionally formication is associated with the sensation of coolness, numbness and pins and needles. It may accompany a reduction in vibratory perception. The feeling of general fatigue and weakness throughout the limbs is a common symptom independent of intermittent claudication.

3 Nutrition of the part in arteriosclerosis obliterans. Observation of the nutrition of the skin, nails and muscles is important Atrophy of the skin and nails and poor growth and brittleness of the nails are often early signs of impaired circulation. Frequently they are overlooked or incorrectly interpreted When noted, especially in patients past 40, they indicate the need for a vascular examination of the extremity. Atrophy of the skin is frequently accompanied by absence of sweating and, in some cases, interference with hair growth. Conversely, as the circulation improves under treatment, evidence of nail and hair growth is a favorable sign. Atrophy of the muscles, with marked reduction in the circumference of the extremity and in the patient's weight, is commonly seen (Fig. 29)

4. Changes of color with postural changes. Relatively early in the presence of arterial deficiency of an extremity there develops the combination of pallor on elevation, and rubor followed by cyanosis on dependency of the extremity. Pallor may be found without rubor and vice versa, it is relatively rare to have one present without at least slight signs of the other. Rubor on dependency without infection is presumptive evidence of vascular impairment. In the presence of infection at least some of the rubor is very apt to persist on elevation of the foot. It should be re-emphasized that palpation of a pulsating dorsalis pedis or

posterior tibial artery does not disprove occlusion of a vessel in the foot peripheral to the point of palpation

As explained previously, the color depends on the blood contained in the minute vessels of the skin and the subcutaneous vessels When the circulation is impaired and the extremity is



Fig 29 —Marked atrophy of the legs secondary to arteriosclerosis *obliterans* in a woman, 60, with tubular narrowing of the arteries of the legs (*From Medichrome Series MM—Vascular Diseases*, by I S Wright and W T Foley)

elevated, the blood drains out quickly into the deep veins and is not replaced rapidly enough to maintain the normal color In severe cases pallor increases to the point where the extremity is pale yellow. On dependency the blood stagnates in the vessels, not moving on because of lack of arterial pulse pressure and other factors At first this results in rubor which becomes cyanosis as the oxygen in the blood is utilized, although if the temperature of the

limb is as low as 10 C. (50 F.), the blood will not part with its oxygen. Minute vessels are damaged by the cold and dilate, and the skin becomes bright red even when the blood flow is slight. Increase of heat, on the other hand, tends to increase the cyanosis if the blood flow to a limb is arrested.

5. Venous filling time. At the time that observations for rubor on dependency are made, the venous filling time should be noted in the following way.

After elevation of the feet above the heart level for a sufficiently long period to cause collapse of the superficial veins, the feet are quickly lowered to the dependent position. The length of time necessary for the veins of the feet to fill and become prominent is noted. Normally this is 10 seconds or less. Longer periods indicate impairment of the arterial or capillary circulation roughly proportionate to the delay.

A word of warning in regard to this test is indicated. The observer must be most careful to be certain that the filling takes place from below upward (from the distal portion centrally) not from above downward, because the latter may be the result of incompetence of venous valves which normally prevent back flow We have seen numerous patients with false normal filling times on this basis, but with severe occlusive arterial disease.

6 Edema Edema rarely, if ever, occurs as a result of arteriosclerosis alone This is logical. The fluid is not dammed back and the venous pressure tends to be decreased rather than increased Edema in the presence of arteriosclerosis obliterans requires careful search for heart disease, kidney disease, thyroid deficiency, venous impairment and nutritional deficiencies, any one or combination of which may explain its presence.

7. Condition of arteries All accessible arteries should be examined for tortuosity, nodules and compressibility. Frequently the arteries are hard, either *uniformly* or in scattered areas, where calcification has taken place. This does not necessarily indicate occlusion, but it is frequently associated with it.

8. Ulcers. The ulcers of arteriosclerosis tend to occur on the

toes, heels or anterior tibial surface. They are usually dry rather than moist unless secondarily infected with either bacteria or some fungus growth Secondary infection is very common. The ulcers tend to extend rather slowly, are frequently undermined at the edges and may develop a black eschar type of base. The degree of pain which they cause varies greatly Large trophic ulcers may cause relatively little pain, whereas a small ulcer, especially if infected, or even a preulcerous area, may produce excruciating



FIG 30 —Gangrenous ulcers due to arteriosclerosis obliterans associated with diabetes mellitus in a man aged 64 (From Medichrome Series MM—Vascular Diseases, by I S Wright and W T Foley)

pain Many of these lesions have as their precipitating factors trauma, such as occurs when a heavy object is dropped on the foot or the toe is stubbed, or too close paring of corns or nails. Each ulcer should be considered actually to represent the first stage of gangrene, since they are produced or perpetuated by inadequate blood supply to the area (Fig. 30).

9 Gangrene The gangrene of arteriosclerosis may be limited to a small area or may be massive, involving a large portion of a limb Its extent depends on the size of the occluded vessel and

other factors, especially infection. Closure of major vessels, as of the femoral arteries, may, however, take place without development of gangrene if the collateral vessels supply the tissues adequately The chief factor in this situation is whether the occlusion has taken place slowly enough to permit the development of adequate collateral circulation

Gangrene may develop as a small bluish spot, commonly on one toe, and gradually spread to involve the entire toe, foot or leg At other times an entire toe may be involved at once owing to occlusion of a digital artery. With occlusion of a major artery an entire limb may turn bluish black at one time. Gangrenous areas may be painless or extremely painful. Exactly why this is, we do not know. If the process is dry and uninfected the involved portion of the extremity may become mummified and tend to self-amputation. Frequently, surgery is necessary to complete the severing process It is necessary to watch the patient's general condition as the gangrenous areas spread. If serious evidence of generalized infection or toxicity develops and does not readily yield to sulfonamides or penicillin, amputation well above the level of occlusion should be carried out promptly. This is especially important in patients with diabetes mellitus and gangrene.

There may be sclerotic plaques along the vessel walls for many years without much interference with the vascular function. Suddenly, however, a thrombus may form around a protruding portion of a plaque, followed by occlusion within a short time. It is frequently difficult to make a differential diagnosis between this process and a true embolic episode, especially in the presence of auricular fibrillation This may to some degree be an academic question with reference to an extremity, since conservative treatment for both conditions is the same. If an embolus has occurred however, anticoagulant therapy should be used to prevent subsequent development of emboli from the same site. If embolic ex

cision is under consideration it is, of course, vital to be certain that an embolus is the more likely probability.

When an aneurysm occurs as a result of arteriosclerosis obliterans, function may be satisfactory for a long time. As it increases, it may cause pain by pressing on the nerves. For example, the popliteal nerve is frequently stretched over a popliteal aneurysm and may be badly damaged as a result of the stress over a protracted period If the aneurysm in a key position such as the popliteal space continues to enlarge, surgery is necessary to avoid such complications as the formation of a large thrombus, portions of which may break off to produce embolic phenomena at the distal portion of the extremity It is usually possible to obliterate the aneurysm without loss of the extremity because with growth of the aneurysm the collateral circulation usually develops to a remarkable degree In other cases the surgeon may attempt venous transplant to replace the portion of artery involved by the aneurysm This procedure has been successful in a number of cases. The transplant is made from a segment of the saphenous vein

Findings by Means of Special Examinations

Certain tests are very helpful in evaluating the degree to which the circulation has been impaired The technics for these special examinations are discussed in detail in Chapter II

Oscillometric readings —These are useful in determining the patency of the major vessels and the level of their occlusion. There has been a tendency in some quarters to overinterpret and to draw unwarranted conclusions from oscillometric studies One cannot determine the type of sclerosis, but the oscillometer will frequently demonstrate good pulsations in the vessels of the foot when palpation has failed to locate the vessels or to disclose a definite pulsation Oscillometric readings have some significance when the two extremities show a marked difference in the readings. For example, the readings on page 130 were obtained in one patient

	RIGHT	LEFT
Over arch of foot	0 25 deg.	0 deg
Above ankle	2	0 5
Below knee	3	1
Above knee	5	2

Inasmuch as both legs were exposed equally to a warm environment, there could be little doubt that there was a definite difference in the patency of the major vessels of the two extremities. Oscillometric readings do not, however, give much information about the collateral circulation. Frequently collateral circulation is adequate despite an abnormally low oscillometric reading, resulting from narrowing or occlusion of the major vessels In other words, the oscillometer may be a valuable aid in the hands of one who understands the evaluation and interpretation of the readings Oscillometric readings must always be made in a room where the patient is warm, since chilling may produce spasm of the vessels and diminished pulsation.

Surface temperature studies.—It is seldom necessary to use a thermocouple to determine whether the skin temperature of one extremity is lower than that of its mate. Under similar conditions, a difference usually indicates impairment of the circulation A difference of even a fraction of 1 degree can be readily recognized by the dorsal surfaces of the examiner's fingers. If one wishes to record the exact difference, temperatures should be taken by means of a thermocouple and potentiometer or a radiant heat measuring unit. To be of value, the readings should be made in a room with constant temperature under carefully controlled conditions.

Reflex vasodilatation test.—To determine the potential vasodilatation it is wise to use some form of reflex vasodilatation or a procaine injection of the sympathetic nerves supplying the extremity under investigation. Various modifications of reflex vasodilatation tests have been proposed. Landis and Gibbons suggested immersing the involved extremities in hot water (43.3–44.3 C.; 110–112 F.) for 20–40 minutes. Maddock suggested wrapping



Fig. 31 (*above*).—Arteriosclerosis obliterans. Definite evidence of involvement of posterior tibial artery, with no change in dorsalis pedis, illustrating the manner in which arteriosclerosis may involve isolated segments of the arterial tree anywhere in the body.

Fig. 32 (*below left*).—Arteriosclerosis obliterans. Definite evidence of involvement of posterior tibial and dorsalis pedis arteries. Although valuable in diagnosis, [illegible]

the patient in blankets and hot water bottles. Application of a heating pad to the abdomen or wrapping of the arms in a heating pad is frequently satisfactory. Sometimes, however, spasm is so



FIG. 34*A*.—Marked calcification of posterior tibial and dorsalis pedis arteries, visualized by soft tissue x-ray technic.

intense that it is not released by these measures. In such cases spinal anesthesia, lumbar ganglionic block, general anesthesia or procaine block of properly selected nerves, for example, the posterior tibial

nerve, will release the spasm and produce marked elevation of the skin temperature of the supplied area.

X-ray studies.—Soft tissue x-ray studies to determine the pres-



FIG. 34B.—Calcification of interdigital arteries of feet, visualized by soft tissue x ray technic.

ence of characteristic pipestem calcification or isolated plaques, and therefore of arteriosclerosis, are recommended. They will not give information regarding patency of the vessels (Figs. 31–34). Atherosclerosis which has not yet calcified may not show in x-ray films.

Arteriography.—We have not found arteriography necessary for the clinical care of arteriosclerosis. However, when a true or

false aneurysm is suspected, arteriography may be justified to determine its location and to gain additional information before surgical intervention (Fig. 35).



FIG 35.—Arteriosclerosis obliterans. Arteriogram showing obliteration of femoral artery in midthigh, with collateral branches carrying blood around the obstruction and back into the artery just above the popliteal space

Histamine flare tests.—In general, histamine flare tests are not necessary for making the diagnosis or for selecting the therapeutic procedures best suited for the particular patient.

Measured work tests—By having the patient climb stairs or walk a certain distance at a fixed pace (for example, 120 paces per minute) and observing the onset of claudication pains and the point beyond which he cannot proceed, valuable information is obtained for comparison with future studies after treatment. Similar, perhaps more accurate, observations can be gained by using one of the various ergometers (p. 51 and Fig 9) or by forcing contraction of the muscles by faradic stimulation (Landis *et al*) until the muscle can no longer function.

When evaluating the results of treatment with reference to intermittent claudication one should be certain that a patient who claims to be able to walk farther is not actually doing this at a markedly reduced pace. In other words, a man who formerly walked rapidly may learn to walk slowly to adjust to his circulatory deficiency and hence report to his doctor that he is now able to walk six blocks instead of two. Such a finding would be very important if he walked at the same rate as he did originally This point must be kept in mind in the evaluation of therapy and justifies the use of an ergometer, which forces the patient to exercise at a specific rate to disclose any actual change.

Treatment

The attitude of hopelessness and discouragement which still prevails among some members of the medical profession with regard to arteriosclerosis obliterans is certain to be reflected in the reaction of the patient to his disease In the course of experience with a large number of patients with circulatory impairment of all degrees, we have found that except in the most extreme cases the prognosis in terms of duration of life and comfort is far better than was formerly believed. Meticulous care by the doctor and the patient, combined with the procedures to be discussed, has resulted in a reduction in the number of amputations and frequently a marked increase in the claudication distance over a period of months and even, indeed, years. Some patients who have followed

a careful régime are able to walk farther and have better oscillometric readings today than was the case 10 years or more ago.

Rest.—Extremities with arteriosclerotic ulceration or impending or actual gangrene should be relieved of any stress or strain. A foot, for example, should not be used for standing or walking When sclerosis is present without trophic changes, ulceration or gangrene, the extremity should be exercised frequently to the point of pain in order to encourage collateral circulation by stimulating the demand for blood supply. It is inadvisable to force the part beyond the point of pain since this will probably result in the accumulation of toxic products and encourage the onset of a gangrenous process Patients without an ulcer or gangrene are instructed to walk to the point of pain a number of times each day.

Position.—In the presence of impaired arterial circulation it is important, as mentioned earlier, that the limb be placed in such a position that it is not higher than the level of the heart. Beds which are theoretically level frequently sag in the middle under the weight of the trunk; the toes are actually above the heart level and are therefore subject to prolonged ischemia during sleep. This must be avoided. It is therefore routine to advise that the head of the bed be elevated 10-12 in This is best done by putting the posts of the head of the bed on wooden blocks maintaining the feet approximately 6 in. below the heart level, the optimal position for any prolonged rest period.

Exercise.—It is important that prolonged complete inactivity be avoided because of the tendency to stagnation of the blood and increased tendency to thrombosis, especially in the veins of the legs Additional ill effects include inadequate nutrition and frequent cramplike muscle pains. For this reason, carefully controlled exercises have been used to encourage the collateral circulation to take over the burden of the supplying tissues. Perhaps the best known are those described by Buerger. They consist in principle of having the patient lie in bed and put the legs through a cycle of elevation, dependency and rest. Instead of setting arbitrary time

periods for all patients we have suggested the following routine as a therapeutic guide

The physician should observe how long it takes for the patient's feet to become pale on elevation The exact length of time necessary for the development of pallor should be the time prescribed for elevation of the feet during the Buerger exercises The feet should then be placed in a position of dependency and the length of time noted for the development of marked rubor This should be the time prescribed for dependency in the Buerger exercises. In other words, instead of arbitrary times, the prescription should be based on physiologic function of the vascular tree of the extremity A complete cycle might be as follows: elevation, 3 minutes, dependency, 2 minutes, rest, 1 minute This cycle should be repeated seven times, as many times a day as the patient is able to carry out the cycle without undue fatigue or claudication pain When one leg is more severely affected than the other, the timing of the cycle should conform with the needs of the more critically involved leg

Arthur Allen has described a helpful series of exercises in which the legs are hung over the edge of the bed and the feet are exercised by flexing and extending the ankles, turning the feet inward and outward, then spreading and closing the toes These probably should not be done in the presence of gangrene. They will produce a marked increase in circulation if adequate main and collateral vessels are functioning

Tobacco—It is now generally recognized that the use of tobacco in the presence of impaired circulation is inadvisable Silbert and others noted that in thromboangiitis obliterans smoking was a marked aggravating, if not indeed the commonest, etiologic factor. Most vascular clinics subscribe to this theory, at least with reference to aggravation Experimental studies by Maddock and Coller, Barker, Wright and Moffat, and Lampson have established the fact that smoking usually causes a diminution of the blood supply to an extremity, normal or otherwise, by constricting the peripheral arteries as determined by thermocouple readings, capillary microscopy and plethysmographic studies. Whether or not there is an

allergic phenomenon has been discussed, but the evidence does not seem conclusive.

So far the only established mechanism is the physiologic one of constriction of the small arteries and arterioles. For the arteriosclerotic patient with circulation already impaired, this is sufficient to interdict the use of tobacco. Although spasm of the major sclerotic vessels is not considered as important in arteriosclerosis obliterans as in some other vascular conditions, one should remember that the life of the tissues in these cases depends on small collateral vessels, that these are usually not sclerotic and that they may be constricted by smoking. For example, if the circulation of an extremity is already impaired to a fraction of its former potential—let us say to where the life of the tissues is in doubt—the smoking of tobacco or exposure to any other factor such as cold which further reduces the circulation may well result in gangrene This principle operates in all degrees and clearly indicates that patients with definitely impaired circulation from arteriosclerosis or any other cause should abstain from the use of tobacco

Alcohol.—Alcohol has definite vasodilating effects on the peripheral arteries. Experiments carried out in our laboratory showed, following the ingestion of 60–90 cc. (2–3 oz) of whisky, a rise in temperature of the tips of the extremities as great as 6–7 degrees (C., 9–12 F.), depending on the condition of the vessels and the control level preceding the experiment. We feel, therefore, that the use of whisky or other spirituous liquors is indicated in the treatment of organic occlusive peripheral vascular diseases, among the most important of which is arteriosclerosis. There is widespread agreement regarding this.

The dosage depends on the severity of the condition and the tolerance of the individual. With impending or actual gangrene the patient should receive enough alcohol, in any palatable form of the patient's choice, to keep the peripheral vessels as dilated as possible. On our service such a patient is often kept slightly

inebriated during the critical period This may require 30–60 cc. (1–2 oz) every four hours or more frequently This amount should be tapered down as the emergency subsides to 1–2 oz. twice a day, which is the dosage usually recommended in nonacute cases Brown and Allen pointed out that, in addition to vasodilating properties, whisky may control the pain in some cases of peripheral vascular disease more satisfactorily than morphine

In diabetics, who comprise a fairly good portion of our patients with extreme atherosclerosis, the alcohol consumption must be calculated within the diabetic diet. Peptic ulcer and alcoholism are, of course, contraindications to its use.

Baths and soaks.—The proper use of baths is an important element in the treatment of arteriosclerosis Four types of baths are most commonly used.

a) Modified sitz bath. In the absence of an open lesion the patient is instructed to sit in a bathtub containing 12 in. of water maintained at a temperature of 37.8 C (100 F.) for 20–30 minutes at least once a day. The heat extends high enough for collateral vessels from the trunk and femoral arteries to be activated If water of this temperature seems to cause discomfort, the temperature should be reduced to 34 4–36 7 C. (94–98 F.)

b) Contrast baths The popularity of contrast baths has diminished in recent years There are several objections to their use First, the best containers can only reach to the knee (most containers do not come that high) and the arterial blockage may be far above knee level Although contrast baths induce important metabolic responses, the ability to respond may not be realized at the level of the stimulus Indeed, the increased metabolic demand in the absence of ability to respond may actually be harmful. Second, vessels already damaged, when forced into sudden vasospasm by the cold water, may remain closed with formation of a thrombus, thereby complicating the picture considerably Third, there is extreme pain occasionally during the cold phase. The modified sitz bath is considered to be somewhat better therapy.

One container holds water at 37.5–40 C. (100–105 F.) and the other, water at 15–20 C. (60–70 F.). The legs are placed first in one and then in the other, alternating at intervals of one to three minutes, repeated about seven times. The last immersion should always be in the warm water. The procedure should be carried out once or twice a day.

c) Whirlpool baths. Whirlpool baths may have some value in the presence of chronic low grade ulceration or early gangrene, the movement of the water helping to clear away crusts and improve drainage. The temperature of the water should be about 35 C. (95 F.)

d) Soaks Wet dressings have largely been abandoned on our service because of their tendency to cool even under the most favorable conditions Cooling produces vasoconstriction and thus does more harm than good by defeating the chief aim of improving the circulation to the dying cells In their stead, for ulcerated or gangrenous extremities for which sitz baths cannot be utilized, we use soaks of normal saline at 35–37.5 C. (95–100 F.) These may be applied for 15–30 minutes two or three times daily After each soak the foot is removed carefully and placed under a warm cradle with the temperature between 31 and 35 C. (88 and 94 F) to avoid chilling. The object is to allow proper drainage by softening and cleaning away crusts which lock in infection.

Once infection is under control, attempts should be made to produce a *dry lesion* rather than a wet macerated one, because healing is more rapid and the danger of infection is reduced when the lesion is dry. Every second or third day it is advisable to substitute for the saline soak a solution of potassium permanganate *1:5,000* at the same temperature. This is to combat fungus infection which frequently hinders the healing process.

Heat.—Heat, properly used, is of great importance in the treatment of arteriosclerosis obliterans. Too frequently *it does far more harm than good* because of improper use. The object is to reproduce normal temperature conditions. Normal surface temperature

rarely exceeds 34–35 C (93–95 F.). To achieve this and to stimulate normal metabolic processes, the temperature of the surrounding environment should approximate that level. We therefore use thermostatically controlled heat cradles (Fig 36) to keep the temperature between 34 and 35.7 C. (92 and 96 F.). Occasionally the pain at these levels lessens at lower temperatures, e.g., 84–88 F. By careful watching and the placing of a thermometer

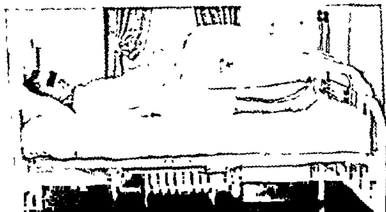


Fig. 36—Thermostatically controlled cradle (Valverde type). Note automatic heating unit at foot of bed and thermometer to provide a double check. Thermometer (arrow) should have been placed nearer the toes to determine more accurately the temperature of that area

equidistant from the heat source and the extremity it is possible to use ordinary light bulbs The risk of error is great, and many cases have been greatly aggravated by overheating As Starr has pointed out, increasing the metabolic demands beyond the capacity of the supplying arteries to provide fresh blood increases the likelihood of gangrene.

Temperature-controlled heat within the limits outlined is, in our opinion, the only safe form of local heat to use in this condition. The local use of heat lamps, diathermy or short wave machines is to be condemned. I have seen more than 70 cases in which severe ulceration or gangrene had been precipitated by

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5,000 units per cc. have controlled infection after other means have failed Experience with sulfonamide powders has not been very favorable because they tend to crust over the wound and act as irritating bodies rather than therapeutic agents. Not infrequently fever and other signs of toxic absorption from the infection in the lower extremity develop. These can become serious and may even be fatal, with or without terminal pneumonia or recognizable bacteremia When fever develops, the use of sulfonamides and penicillin must be considered. We have used penicillin in doses of *300,000–1,000,000 units a day in such cases* with very satisfactory results. An ointment we use at present contains 5,000–10,000 units of penicillin per 30 Gm (1 oz) in a petrolatum base This is applied only when it is necessary to soften calloused skin and at the same time have an antibiotic agent present Penicillin should be applied locally with caution in the presence of fungus infection. It some times greatly aggravates such lesions

Pressure-suction boot treatment—The pressure-suction boot providing variations in environmental pressure by hand pumps was used in the treatment of impaired circulation before 1500 Landis and Gibbon, and Herrmann popularized the procedure and perfected mechanical apparatus to make the pressure changes automatic The hypothesis is that the blood flow to an extremity can be increased markedly by exposing the extremity to fluctuations in pressure from positive to negative and back to positive, continuing such alternations for the duration of the treatment, which may be from one hour to several days

The extremity is contained in a so-called boot of glass or metal in which pressure changes are produced by means of a connection through an air pump system The opening through which the leg is inserted is made air-tight by means of a rubber cuff There has been considerable disagreement as to the type and timing to be used and the amount of suction and pressure desirable The cycle most generally used is that suggested by Herrmann Accepting the base line as atmospheric pressure (760 mm), one complete cycle

measures producing excessive heat. Seven patients lost their legs and two died, not as a result of their arteriosclerosis, but rather as a result of misapplied treatment. In contrast, reflex heat produced by applying heating pads or other forms of heat to the abdomen or sacral area is helpful without being dangerous. We frequently recommend the use of electric heating pads on the abdomen for one hour three or four times daily. They should never be applied to extremities with impaired circulation. There seems no evidence to justify keeping the extremities at room temperature

Anticoagulants.—The use of anticoagulants, including heparin, Dicumarol and Tromexan, for arteriosclerosis has largely been confined to patients with sudden occlusion on the basis of thrombosis or embolism. Their importance in the modern treatment of coronary thrombosis with myocardial infarction has been demonstrated. It is known that anticoagulants will interfere with the propagation of a thrombus and will reduce the incidence of embolic phenomena It is also known that prolonged rest, which is necessary for some of the patients with gangrene with resultant stagnation of the blood on the basis of arteriosclerosis obliterans, encourages thrombosis in both the arterial and the venous tree. Anticoagulant therapy is indicated when there is a tendency to propagation of thrombi or repeated embolic episodes. (See Chap. XX for details)

Antibiotic and sulfonamide therapy.—The frequency with which infections complicate arteriosclerosis obliterans is well known. Although the primary consideration is the impaired circulation, the tendency to infection must never be forgotten, and particularly with diabetic gangrene. The cultures from the lesions often produce a mixed growth, making it difficult to decide on the drug to use to combat the organisms responsible for the infection. Usually wet soaks, including potassium permanganate soaks, will solve the problem of the infection. The use of strong antiseptics is definitely contraindicated.

In some cases wet dressings with penicillin solutions of 500-

after several days the skin becomes mottled and blistered. In these groups the results of its use may be serious

Intermittent venous hyperemia.—Lewis and Grant demonstrated that, after occlusion of the arterial blood flow by a tourniquet for 15–20 minutes or more, release of the tourniquet not only caused the blood flow to return to normal but produced a hyperemia, sometimes to as much as 600 per cent above normal Later studies, however, showed that the excess merely made up the deficit that had accumulated during the preceding period of tourniquet constriction

On the basis of Lewis and Grant's observations, Collens and Wilensky devised an apparatus to produce a state of venous stasis and release in cycles of about two minutes by means of a blood pressure type of cuff around the limb which is alternately inflated and deflated by a motorized pump The degree of inflation can be controlled, 30–80 mm. Hg of pressure usually being used. In our opinion there is no close parallel between the experiment of Lewis and Grant and the apparatus of Collens and Wilensky as it has been used The latter workers reported very favorable results in the treatment of arteriosclerotic claudication and gangrene and in thromboangiitis obliterans. We have been unable to duplicate the results, nor have others, including Allen and his co-workers at Mayo Clinic, and it appears that this equipment is being used much less than formerly.

Oscillating bed.—A form of mechanized treatment which is being used with increasing frequency is the motor bed described by Sanders (Fig 37) By means of this so-called vasoscillating bed, the head and feet of the patient are alternately elevated and lowered, a complete cycle taking 1–2½ minutes Movement is smooth The degree of tilting and the speed of the cycle can be regulated within reasonable limits The most common satisfactory cycle is one in which the foot of the bed rises 6 in. above the horizontal and descends 12–15 in

A new type of oscillating bed, known as the Minnenberg bed,

takes 15 seconds: the first three seconds are of positive pressure, gradually reaching 20 mm. Hg; there is then a gradual reduction of pressure, crossing the base line and proceeding to a negative pressure of —80 mm. Hg; more rapid return to the base line completes the cycle in 15 seconds. This is repeated continuously for the duration of treatment. For efficient operation of the boot the cuff around the extremity must be air-tight. This produces some constriction around the limb and hence interferes with the blood flow, especially that in the superficial vessels. Many types of cuffs have been devised in attempts to overcome this objection.

In general, when the circulation of an extremity is increased, there is an increase in its surface temperature. However, we and others have noted that the temperature of an extremity was often lower following the treatment than before. This may have been due to the constriction by the cuff or in part to the continuous flow of air in and out of the boot. Therefore reflex heat, such as application of a heating pad to the abdomen, was used in an attempt to improve the circulation The degree of vasodilatation from reflex heat depends on the potential capacity of the vessels still capable of functioning in a limb.

The first optimistic claims for this method included therapeutic value in arteriosclerosis, senescence diabetes, thromboangiitis obliterans, Raynaud's disease, acute embolus, frostbite and other forms of circulatory impairment. Experience, however, has greatly narrowed its indications. In fact, we no longer use it in the treatment of vascular diseases and its use has markedly decreased in the past several years.

Pressure-suction is definitely contraindicated in cases of acute or subacute *infectious* processes, any form of acute or subacute thrombophlebitis (present in a large percentage of cases of thromboangiitis obliterans) or in the presence of any evidence of autolysis of the tissues such as that noted in cases of acute embolism and thrombosis, e.g., arteriosclerotic sudden occlusion in which

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A new type of oscillating bed, known as the Munsterberg bed,

takes 15 seconds: the first three seconds are of positive pressure, gradually reaching 20 mm Hg; there is then a gradual reduction of pressure, crossing the base line and proceeding to a negative pressure of —80 mm. Hg; more rapid return to the base line completes the cycle in 15 seconds. This is repeated continuously for the duration of treatment. For efficient operation of the boot the cuff around the extremity must be air-tight. This produces some constriction around the limb and hence interferes with the blood flow, especially that in the superficial vessels Many types of cuffs have been devised in attempts to overcome this objection

In general, when the circulation of an extremity is increased, there is an increase in its surface temperature. However, we and others have noted that the temperature of an extremity was often lower following the treatment than before. This may have been due to the constriction by the cuff or in part to the continuous flow of air in and out of the boot Therefore reflex heat, such as application of a heating pad to the abdomen, was used in an attempt to improve the circulation. The degree of vasodilatation from reflex heat depends on the potential capacity of the vessels still capable of functioning in a limb.

The first optimistic claims for this method included therapeutic value in arteriosclerosis, senescence diabetes, thromboangiitis obliterans, Raynaud's disease, acute embolus, frostbite and other forms of circulatory impairment. Experience, however, has greatly narrowed its indications. In fact, we no longer use it in the treatment of vascular diseases and its use has markedly decreased in the past several years.

Pressure-suction is definitely contraindicated in cases of acute or subacute infectious processes, any form of acute or subacute thrombophlebitis (present in a large percentage of cases of thromboangiitis obliterans) or in the presence of any evidence of autolysis of the tissues such as that noted in cases of acute embolism and thrombosis, e g., arteriosclerotic sudden occlusion in which

er temperature seems to make the patient needlessly uncomfortable.

The patient soon becomes accustomed to the motion, and I have had patients who have slept voluntarily on such a bed at night for as long as five years When first seen, most of these patients were in an extremely serious condition, with total occlusion of the major arteries up to the inguinal area. They were hospitalized and placed on an oscillating bed for a month. They were then permitted to return home, where they continued to use the oscillating bed and were gradually allowed greater activity.

A woman, who for over two years was unable to walk more than 100 ft, improved to the point where she could go dove shooting and walk across fields for as much as half a mile. From being a semi-invalid she improved to the point of being an active person with only moderate restrictions and lived for a number of years thereafter, to die later of a carcinoma of the esophagus. She continued during the last years of her life to sleep on the oscillating bed each night, thus giving herself vascular exercises for approximately 8–10 hours out of each 24 With the change of the seasons the bed was shipped from her winter to her summer residence

The process is gentle, does not involve the use of constricting bands and is physiologically sound, especially in the treatment of arteriosclerosis both with and without gangrene It has the additional advantage of preventing the stagnation of blood in the veins of the legs and thus reduces the tendency to phlebothrombosis or thrombophlebitis. It also tends to prevent the decalcification which occurs during long periods of static illness Ulcers have healed after complete failure of the pressure-suction boot, the intermittent venous hyperemia apparatus and other mechanisms The total usefulness of the oscillating bed is somewhat impaired by the fact that it is expensive both to buy and to rent and that the patient must be prepared to utilize it for a protracted period. Clinically it is standing the test of experience.

Saline and other solutions intravenously.—Following the use of normal and hypertonic saline solutions for treatment of throm-

has had extensive trial. The fulcrum, instead of being in the center, is at the head of the bed, the change in position being produced by the raising and lowering of the foot of the bed by a

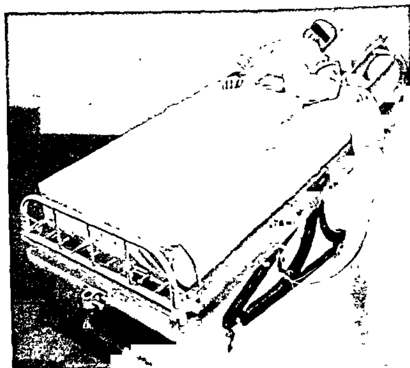


FIG 37.—Sanders vasoscillating bed (Courtesy of American Hospital Supply Corp.) A thermostatic cradle (see Fig 34) is frequently used in conjunction with this type of bed

lifting mechanism. This equipment is standing the test of time and we are using it at present with complete satisfaction.

The object is to exercise the arteries still able to function by producing rubor and pallor (engorgement and ischemia) in a manner similar to Buerger's exercises, continuously and without fatiguing the patient. We usually use a thermostatically controlled cradle with the temperature at 35–37.5 C. (93–96 F.) as adjunct treatment. The temperature may be lowered to 33–34 C. if the high-

as sympatholytic agents nullify sympathetic nerve transmission, usual reference being to adrenergic pathways controlling blood vessels and the usual site of action at the end-organ. A sympatholytic drug must be adrenolytic, but the reverse is not necessarily true, for certain drugs may be adrenolytic only. Other agents may interrupt sympathetic nerve transmission by acting directly on ganglions without antagonizing epinephrine.

Priscoline (Priscol) (2-benzyl-4-5-imidazoline hydrochloride), Dibenamine hydrochloride and Roniacol act as adrenolytic and sympatholytic drugs. *Tetraethylammonium chloride (Etamon chloride)* differs from these drugs in that it acts as a generalized ganglionic blocking agent and is not adrenolytic. It also interferes with the parasympathetic transmission Its effects are interrupted by neostigmine All of these drugs have been used in the treatment of peripheral vascular disease, including arteriosclerosis obliterans, but Priscoline has been used most widely It may be administered orally or intravenously The usual dose is 25–50 mg. three to six times a day It is given in peripheral vascular disease in the hope of releasing vasoconstriction of the vessels able to dilate, thus increasing blood flow in an affected limb.

There is some favorable evidence for this action but also some question as to whether, when a drug producing generalized vasodilation is used, the affected leg does receive any specific increase in blood flow, especially since the rest of the peripheral vessels are able to respond in a more normal fashion The therapeutic effect of all of these drugs in arteriosclerosis obliterans is far from clear. Untoward effects from their use include excessive drops in blood pressure, palpitation, "goose flesh," itching of the scalp, other peculiar sensations of the skin, nausea and activation of peptic ulcers Many patients cannot continue their use.

On the other hand, some patients may take any of these drugs *without any reaction whatever.* Why this is so is not at all clear. Occasionally a patient may not be able to take Priscoline but may tolerate Roniacol without difficulty. The determination of therapeu-

boangitis obliterans, some workers adopted this form of therapy for arteriosclerosis obliterans There are no satisfactory theoretical grounds for it and the therapeutic explanations do not, in our opinion, warrant acceptance of this procedure.

Vasodilating drugs.—Numerous drugs have been used in the treatment of arteriosclerosis obliterans on the basis of their vasodilating powers. Those most commonly used may be divided roughly into the nitrates and allied compounds, the theobromines, theocalcines and allied compounds, the choline compounds, and papaverine. After years of clinical and experimental study with all these groups, it seems fair to state that their value singly or collectively in the treatment of arteriosclerosis obliterans is very limited Briefly, the action of the nitrates is too fleeting and the dilatation in the extremities is observed only with difficulty. The action of theobromine and related compounds in the usual dosages is highly unreliable and doubtful Certain choline compounds, while of established value in some diseases of the peripheral circulation, appear ineffective in arteriosclerosis.

Papaverine has been recommended for the relief of sudden occlusion because of its vasodilating properties. In my experience, in the usual dose given orally or intravenously its vasodilating effects are highly unreliable and not nearly as marked as those from simple reflex heat or whisky. Further studies with larger doses are being carried on. In the treatment of sudden occlusion the injection intra-arterially of 1 gr. (0.06 Gm) in 5–10 cc. of distilled water has in some of our patients given more striking evidence of vasodilatation than that produced by lumbar ganglion procaine block. This deserves more study. The relaxing effects of this and other opiates are well recognized, and the relaxation is undoubtedly valuable. The possibility of ultimate habituation is a consideration in patients who have a long-standing chronic disease.

Adrenolytic, sympatholytic and ganglionic blocking drugs.—Adrenolytic agents nullify important effects of epinephrine where-

diet and metabolism is accomplished early. (4) The very strict diet of Kempner has lowered the serum cholesterol levels of some patients (5) A strict low fat, low cholesterol diet has in some individuals decreased the concentration or even caused the disappearance of the Gofman large cholesterol molecules. (6) A reduction in the mortality rate from circulatory diseases did occur during the starvation period in Norway during the Nazi occupation. Unfortunately this evidence is far from conclusive, and there is no proof that in man the cholesterol in the diet plays a significant role in the prevention or production of atheroma.

Studies with tagged elements have shown that cholesterol can be synthesized in the liver, spleen, skin, wall of the small intestine and most other tissues except the red blood cells The amount thus produced daily is greater than would be ingested in a normal diet The cholesterol levels in the blood appear to be less influenced by the cholesterol intake than by the metabolic processes within the tissues. In diseases in which the blood cholesterol value is consistently high, reduction can rarely be brought about by dietary restrictions without correction of the fundamental metabolic fault

Ancel Keyes has shown that by the combined low cholesterol, almost fat-free diet, a definite drop in serum cholesterol can be obtained The fat intake appears to be at least as important as the cholesterol intake since it seems probable that the sources of the synthesized cholesterol are largely from animal and vegetable fats.

Barr found that moderate restrictions do not significantly alter the levels or distribution of cholesterol or the relationships of cholesterol to phospholipids or protein

There is, therefore, inadequate evidence that dietary restriction affects the course of human atherosclerosis Even the most optimistic view suggests that were the dietary approach to be adopted the restriction of cholesterol and fats should be practically total and should begin in early childhood rather than after the patient has a badly involved vascular system and several occlusions. Such a deprivation over a period of years might well be injurious. This

tic value is extremely difficult and final evaluation must await greater experience

Histidine and ascorbic acid.—These drugs in combination have been enthusiastically advocated by Wirtschafter and Widmann for the treatment of gangrene. Unfortunately, numerous other workers have failed to obtain similar results.

Mufson has used histamine intra-arterially and has reported favorably regarding its effects It has been tried in our clinic and elsewhere, but we would withhold final judgment at this time

Ether.—R A. Katz has advocated the intravenous administration of ether. Except for temporary relief of pain, others have failed to be impressed by the results. Cerebral and pulmonary fat emboli have been reported following this therapy.

Potassium iodide.—This has long been used in the treatment of arteriosclerosis. Striking clinical results have not been obtained, although animal work seems to demonstrate that it tends to prevent the laying down of cholesterol plaques.

Choline and inositol.—Choline and inositol in various combinations have been proposed for the treatment of arteriosclerosis, especially atherosclerosis Three years of study and observation have led us to the conclusion that the claims which were advanced were unjustified and that these substances are worthless for this purpose. Similar conclusions have been drawn by other workers also, based on studies in animals as well as man.

Diet.—The value of restrictive diets for the prevention or treatment of atherosclerosis is still highly debatable. The following evidence suggests that a low cholesterol, low fat diet might prevent the deposit of atheromatous plaques or even encourage their reabsorption (1) Hypercholesteremia can produce atheroma in previously healthy arteries. (2) Some atherosclerotic patients have hypercholesteremia or other lipid disturbance. (3) Kendall has shown that in dogs in which he has produced atherosclerosis by feeding cholesterol and inducing hypothyroidism with thiouracil, he has been able to reverse this process if the return to a normal

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aspect of the problem has been neglected and requires further study.

Advice therefore is difficult. We place all overweight patients or patients with hypercholesteremia on low cholesterol, low fat diets and attempt to correct their metabolic abnormalities pending further studies in this dynamic field. We do not agree with those who do not strive for adequate control of diabetes mellitus in these patients, we strive by diet and insulin to obtain an approximation to normal metabolism and physiology.

Quinine sulfate.—In doses of 0.2 Gm. at bedtime and sometimes also at suppertime, quinine may relieve night cramps in the leg muscles of some patients.

SURGICAL ASPECTS

The technics of surgical procedures are not within the scope of this book. Nevertheless certain established principles should be mentioned. The use of wet dressings, hot soaks and antiseptics has been discussed. To re-emphasize: (1) Wet dressings should not be used unless they are kept warm (34.4–37.8 C.; 94–100 F.). Chilling should be avoided and the tissues should not be permitted to become macerated and boggy. In general, unless infection is present, gangrenous areas should be kept dry between soaks. (2) Warm soaks are usually preferable to wet dressings. The temperature should be 34–38 C. and they should be used once or twice a day for 30–60 minutes. (3) Strong antiseptics should not be used, since the life of the cells of the endothelial buds is the most important single factor in the healing process.

Ganglionectomy and other operations designed to produce vasodilatation, are, in my experience, of limited value in arteriosclerosis obliterans. We have studied the effects of ganglionectomy for arteriosclerosis obliterans for an additional five years since the first edition of this book and have come to the following conclusions. (1) The optimistic claims of some exponents of this surgery are not justified. (2) Its effects on intermittent claudication are no

better than those produced by suggestive therapy or placebos A patient who had no improvement following a sympathectomy was told four years later for the first time to stop smoking and his claudication distance promptly lengthened. (3) The effects on advanced arteriosclerosis obliterans with gangrene are usually nil. (4) In very rare cases when a single toe becomes cyanotic due to occlusion or spasm of a digital vessel, and in the presence of patent major vessels down into the leg or foot, ganglionectomy may produce a favorable response with return of normal color or warmth to the toe. (5) It is unfortunate that many elderly patients have been submitted to operations of this type without adequate study and discrimination. Periarterial sympathectomy is useless and has been abandoned

Peripheral sympathectomy by crushing, alcohol injection or *section of mixed nerves supplying the feet may relieve the pain* but produces paresthesias, a fact not to be overlooked. For the technic for these procedures the reader is referred to the work of Smithwick and White, and Laskey and Silbert These procedures are rarely necessary and should not be used in the upper extremities because the motor fibers are destroyed along with the sensory fibers; whereas this is not so vital in the small intrinsic muscles of the foot, it is serious in the hands Also, unless the nerves are severed there is usually a regrowth of the nerve fibers in four to six months. The operation should be performed with utmost care to avoid trauma to the tissues, leading to difficult healing because of impaired circulation which may be a factor high above the level of the gangrene. Exact knowledge of the location and possible variations of the nerve and of the tissues supplied by each nerve is essential to success. Even then the presence of unpredictable aberrant branches and nerve fibers may cause unsatisfactory results, the pain being inadequately relieved.

Care of gangrene and ulcers—One of the most important factors in management is meticulous care of the ulcers and gangrenous areas by both the doctor and the patient. It is essential

to lift away crusts under which unsuspected pus may accumulate For example, the nail was easily lifted away from the left first toe of a patient to reveal a mass of pus and a large necrotic area. Three months later the ulcer was completely healed. The patient had been under the care of a doctor for months and in a hospital for three weeks, yet the simplest procedure—the institution of drainage without the need for incision—had been completely neglected, with great damage to this arteriosclerotic patient. If this simple principle is ignored the infection may burrow deep into the tissues and spread rapidly.

Sloughing tendons and sequestra from the bones should be carefully removed. This can be done without major surgical technic but it must be done under full surgical asepsis. X-ray evidence of so-called osteomyelitis does not necessarily mean that healing cannot be obtained over the area The apparent osteomyelitis is often due entirely to ischemia and with re-establishment of the blood supply is likely to heal. Frequently it gives rise to sequestra Grayish slough should be meticulously removed one portion at a time. The object is to obtain a base covered by fresh granulation tissue on which epithelium readily forms. Once adequate circulation is available, this may be further encouraged by the proper use of skin grafts.

Amputation—Proper selection of the site for amputation is vital to successful healing. The day of amputating slightly above the level of the gangrene, whether in toe or foot, just because the skin looks good is past. Frequently the tissues under that innocent-appearing skin are sadly undernourished and the skin itself is too poorly supplied with blood to allow healing. This practice leads to repeated amputations, increased mortality and prolonged invalidism. In general, unless necessitated by severe pain or serious infection, amputation should be delayed until nature has done her best to demarcate the area involved, to localize the infection and to attempt some self-amputation If self-amputation has progressed sufficiently in the toes, it is frequently possible to lift away

the toes without surgical intervention. Sometimes moderate help from the surgeon will complete the job and lead to earlier local healing.

If the infection fails to localize and gangrene continues to spread, or if there is a systemic reaction from septic absorption, amputation is the only recourse, but this should not be done until thorough study has determined the level at which healing can reasonably be expected. For this we use modern methods instead of guesswork. The oscillometer will show where the major vessels are occluded; lacking additional data, it is unsafe to operate below that level Arteriographic studies with Thorotrast or Diodrast may give information on the level of blockage of the major vessels and the degree of collateral circulation present. At times we are encouraged to operate below the level of major blockage if the collateral circulation is extensive. This is frequently the case at the knee, where the major blockage may be just proximal to the joint and amputation below the knee may be satisfactory.

If the surgeon is experienced in this field it is probably wise to allow him to use his judgment at the time of the operation. For example, an incision below the knee may reveal a very good blood supply which will probably permit satisfactory healing; or practically no bleeding may occur, in which case it may be safer to perform the amputation at a higher level, even above the knee

Refrigeration.—Our experience suggests that refrigeration is unlikely to aid in the preservation of a limb in which the circulation is badly impaired. It hardly seems logical to induce greater vasoconstriction, increasing the ischemia of tissues already suffering from lack of blood, in order to save them. We, therefore, do not advocate the use of refrigeration in an attempt to save a leg However, if the leg is to be amputated and active infection is present, or if the patient is aged or severely diabetic, refrigeration anesthesia is very helpful and can be used with a minimum of trauma to the patient.

By using the technics described here one can effectively reduce

the number of reamputations and thereby the mortality from amputations. This represents a sound approach to the problem of amputation, which at best is an admission of defeat—an acknowledgment of our inability to save the extremity for future use

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CHAPTER IV. Thromboangiitis Obliterans

Etiologic Considerations

It is impossible to state positively that there is a single agent responsible for the development of thromboangiitis obliterans. That tobacco and sex are among the most important factors has been recognized clinically for many years and recently substantiated.

Tobacco—Erb, Meyer, Buerger and many others realized early that tobacco was at least an aggravating factor. Of over a thousand cases of thromboangiitis obliterans, Silbert has never seen a typical case in a nonsmoker Our group and others have had similar experience The disease has been reported in nonsmokers, but most of these reports were published over 15 years ago and would not stand up under present critical analysis Among 150 patients with the disease, Jones found approximately equal use of American and imported tobaccos.

It is, furthermore, generally accepted that the course of the disease in an individual patient is significantly influenced by his use of tobacco. Specifically, the disease can be arrested in many patients, especially in the early stages, solely by abstinence from tobacco In severe cases with gangrene or ulceration, after days or weeks of satisfactory improvement the smoking of one or two cigarets may suddenly worsen the course of the disease with the appearance of inflammation and breakdown of more tissue. Also, patients whose ulcers have healed and whose condition has been

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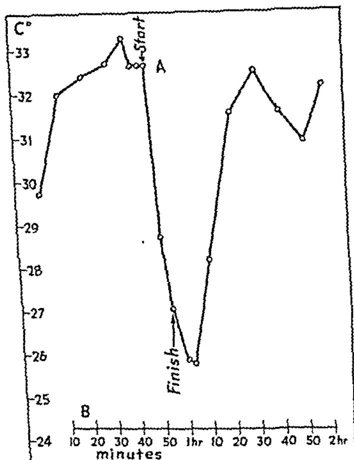


FIG 38.—Surface temperature at finger tips of normal subject after smoking a single "standard" cigaret *A*, fourth terminal phalanx of left hand, *B*, room temperature.

2. The foregoing observations have been further confirmed by Lampson, using plethysmographic measure of the blood flow in cubic centimeters per minute per hundred cubic centimeters of hand (Fig 41). This showed the drop in blood flow to be precipitous

arrested tend to maintain the improvement indefinitely, unless exposed to frostbite or other trauma, so long as they do not smoke In numerous instances the smoking of one to six cigarets has caused a relapse and the loss of a digit before the disease could again be arrested. Therefore the clinical evidence of a definite relationship between smoking and thromboangiitis obliterans has been established.

Attempts to explain the mechanism by which tobacco exerts its harmful effects have been of three types.

1 That smoking causes a vasoconstriction of the peripheral blood vessels of the extremities was demonstrated by studies with thermocouples and capillary microscopy. The temperature of the skin of the finger-tips of most individuals drops with the smoking of one or two cigarets, especially if they are inhaled (Fig. 38). In 135 experiments conducted in our laboratory with the collaboration of Moffat, normal smokers used standard brands of cigarets The drop averaged 5.3 degrees (F.; 4 C.) and in some was as much as 15 degrees (F; 8.5 C.). With so-called denicotinized cigarets containing about 40 per cent of the nicotine in standard brands, the drop in temperature averaged 4 8 degrees (F.; 3 C) (Fig 39). The effect of mentholated cigarets was the same as that of the standard brands (Fig. 40). Similar reductions could not be reproduced by using filter paper cigarets or cigarets made of chopped up cigaret papers. In some individuals the blood flow in the nail fold capillaries could be observed to slow down and stop following the first few inhalations The psychologic factors were eliminated as much as was possible throughout the experiments.

We observed, as others later did, that a slight drop in temperature and a slowing of capillary blood flow may occur after extremely deep inhalations of air alone, but we have not succeeded in producing reductions comparable to those recorded on inhalation of cigarets. Maddock and Coller, Barker, Roth and others have reported similar results.

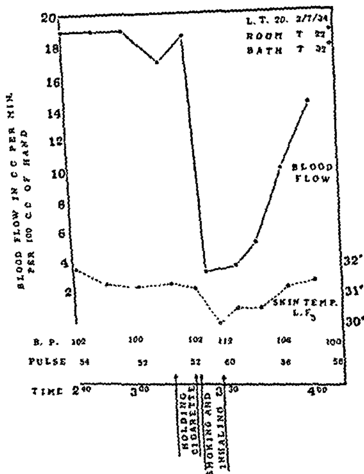


FIG 42.—Effect of inhaling one cigaret, measured by Lampson apparatus *Solid line, blood flow in cc./min./100 cc of hand, dotted line, peripheral skin temperature*

Westcott and I therefore selected 35 carefully studied patients with typical thromboangiitis obliterans and, for controls, 35 persons who had various other diseases or were normal. These were tested with tobacco extracts supplied by Dr. Harkavy and other

mechanisms of action: *(a)* direct action of nicotine on the adrenal glands; *(b)* action on brain centers either separately for two effects, namely, vasoconstriction directly plus the adrenalin effect, or on one area controlling the adrenal glands; *(c)* separate action on nerve endings producing constriction of vessels. There is no conclusive evidence regarding this mechanism.

3 Another approach to the study of the relation of tobacco and thromboangiitis obliterans has been on the basis of an allergic

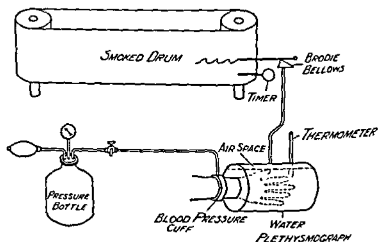


FIG 41 —Apparatus for plethysmographic measure of blood flow (Lampson)

response. Harkavy and his co-workers have reported that individuals with thromboangiitis obliterans have a high degree of hypersensitivity to tobacco as determined by skin tests. They noted reactions in 70 per cent or more patients with thromboangiitis and in 38 per cent or less of controls. Trasoff, Blumstein and Marks reported diametrically opposite results, observing positive reactions in 16 per cent of patients with thromboangiitis obliterans and in 34 per cent of their controls. Chobot reported 52.9 per cent positive reactions to tobacco in asthmatic children, none of whom smoked or had thromboangiitis obliterans.

cate, however, that no specific relationship has been established between thromboangiitis obliterans and sensitivity to tobacco on an allergic basis.

Sex.—There seems little doubt that sex is an important factor in thromboangiitis obliterans. Even though smoking has been

TABLE 4.—POSITIVE REACTIONS TO SKIN TESTS WITH TOBACCO IN NORMALS AND PATIENTS WITH THROMBOANGIITIS OBLITERANS

AUTHORS	THROMBOANGIITIS OBLITERANS		CARDIOVASCULAR DISEASES		CONTROLS	
	No	% Pos	No	% Pos	No	% Pos
Harkavy and Romanoff	69	78*	36	36		
smokers					200	38†
Sulzberger	13	78‡	73	22		
smokers					95	36
nonsmokers					38	16
Trasoff, Blumstein and Marks	31	16	23	13		
normal smokers					40	47
normal nonsmokers					52	21
allergic smokers					17	47 } 34
allergic nonsmokers					21	25 }
Chobot						
asthmatic children					53	89
Westcott and Wright	35	43			35	46
smokers	35	43			24	50
nonsmokers	0	0			11	36
allergic§	5	60			9	67
nonallergic	30	40			26	39

* 9% also positive for other allergens.
† 27% also positive for other allergens.
‡ 15% also positive for other allergens.
§ Family or personal history

prevalent among women for a considerable number of years and the recently reported cases of thromboangiitis obliterans in women have been in smokers, less than 60 cases in women were reported up to 1946. There now appears to be a steady increase in women, which may be related to the increase in smoking. A typical case in a woman follows.

A Russian Jewess, aged 46, was first seen on Nov. 27, 1934. One year previously, after exposing her bare feet to the floor of a cold room, she noticed a burning sensation in the distal half of her left foot. The con-

tobacco extracts prepared in the allergy clinic of New York Post-Graduate Medical School and Hospital. Certain common allergens were used as controls (Fig. 44). Patients tested by Harkavy were observed and the interpretation of reactions was carefully considered In our series the positive incidence of reactions was almost identical in the two groups, being 43 per cent in the

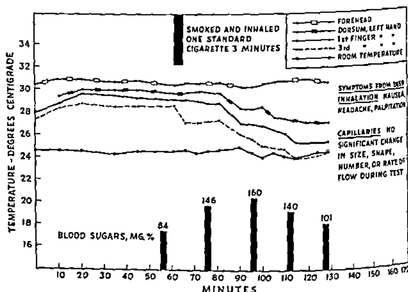


Fig 43—Blood sugar levels after smoking one cigaret by man, 54, with generalized arteriosclerosis, recent coronary occlusion and peripheral sclerosis with intermittent claudication. Hands were exposed at room temperature for one-half hour before readings were made Blood for sugar determinations was taken from right antecubital vein, capillary studies were made on fingers of right hand. Breakfast, of prunes and coffee, was eaten three hours before first blood specimen was taken, cigaret was smoked two hours before readings were begun

thromboangiitis obliterans cases and 48 per cent in the controls (Table 4). Harkavy has accepted slight and slightly moderate reactions as positive, which does not conform with the standard, generally accepted interpretations This accounts for much of the discrepancy in results in thromboangiitis obliterans, although the differences in the controls are still unexplained. The results indi-

The history was essentially negative, except that in 1930 the fifth finger of her right hand had been amputated because of osteomyelitis associated with what was thought to be an acute infection She had smoked from eight to 30 cigarets a day since she was 8 years old. Rye bread was included in the daily diet. She denied using alcohol

Physical examination revealed an obese, well developed female, 59 in tall, weighing 160 lb Blood pressure was 130/90 mm. Hg General examination gave essentially negative results

The extremities revealed marked rubor of both feet on dependency, most prominent over the toes and inner aspect of the left foot Pallor was present on elevation The nail of the first toe of the left foot was

TABLE 5 —Oscillometric Readings

	Left	Right
Dorsalis pedis (arch of foot)	0	0
Proximal to ankle	0	0 5° *at 100 mm Hg* pressure
Distal to knee	1 75° at 100 mm. Hg pressure	2° at 100 mm Hg pressure
Proximal to wrist	0	0.5° at 100 mm. Hg pressure

greatly hypertrophied. Two small, moist ulcers were present under the toes of the left foot, the larger one at the base of the fifth toe Both feet were moderately cold Examination failed to reveal pulsations of the dorsalis pedis artery of either foot or of the posterior tibial or popliteal arteries *of the left leg* The right posterior tibial and popliteal arteries were palpable The radial and ulnar vessels of the left arm were not palpable Both vessels could be felt in the right wrist Oscillometric readings are shown in Table 5.

The routine complete blood count, tests for blood sugar, urinalysis, and blood tests for syphilis gave negative results The electrocardiogram was negative except for a rapid rate of 101 per minute Roentgenograms of the lower extremities revealed no evidence of arteriosclerotic plaques. No abnormal changes were noted on examination of the eyes A Landis hot water immersion test was not performed until Jan 27, 1936 (Table 6) This suggested the establishment of good collateral circulation, in view of the oscillometric readings, which had remained the same as on earlier study (Table 5)

Special typhoid vaccine (100,000,000 per 1 cc ; Kirk Biological Laboratories) was given intravenously, starting with a dose of 10,000,000 and increasing gradually to 70,000,000 The injections caused a 2-3

dition progressed, so that on admission she complained of a constant burning pain over the sole and medial aspect of the foot. Moderate re lief was afforded by heat, but the condition was greatly aggravated by cold During the four months before admission, walking one block had

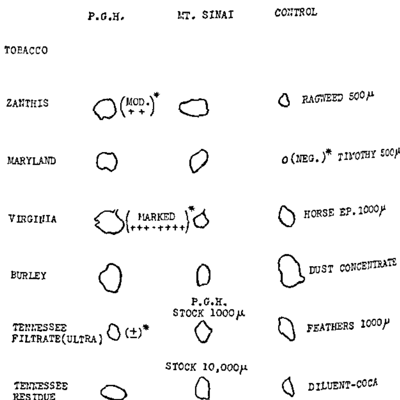


Fig 44 —Tracings of skin reactions to tobacco extracts and to common allergens used as controls *P G H*, extracts supplied by Allergy Clinic, New York Post Graduate Hospital, *M.S*, extracts supplied by Dr. J. Harkavy, Mount Sinai Hospital, New York, asterisk (*), typical readings

caused an aching pain in the left foot and ankle that was relieved only after a few minutes of rest. Two small ulcers beneath and between the last two toes of the left foot had been present for four weeks. One week before admission she had noted a dull pain in her left hand and fore arm somewhat similar to that in the sole but less severe.

burning type and she had severe rest pains (8) She also had claudication as a residual symptom after the ulcers healed. (9) The ulcers were deep, moist, located between the last two toes of her left foot and excruciatingly tender (10) There were marked rubor on dependency and pallor on elevation. (11) There was widespread involvement of the peripheral arteries, indicated by absence of pulsation of certain major arteries supplying both feet and the left hand. (12) There was prompt response to abstinence from tobacco and intravenous typhoid therapy, with healing of the ulcers, even though the patient was ambulatory (13) Her syndrome became repeatedly aggravated upon the resumption of smoking

Of the theories advanced to explain the rarity of this disease in women, three seem worthy of note (1) differences in the habits and exposure of the two sexes, (2) a sex-linked hereditary factor, and (3) a biologic difference which provides women with an immunity. The first theory has been mentioned in the discussion of tobacco and is discussed further under the heading of trauma To my knowledge no work of importance has been presented regarding the second theory

With reference to the third theory, Friedlander, Laskey and Silbert studied the blood volume, cholesterol values, fibrinogen content and viscosity before and after bilateral oophorectomy in women and in female cats. They reported a consistent postoperative reduction in blood volume of about 25 per cent and a coincidental increase in cholesterol and fibrinogen content and viscosity in both species A corresponding study of controls with artificial and natural menopause showed no changes in blood volume or chemistry That oophorectomy is not in itself enough to produce the disease is readily established by the rarity of the disease in women following such a procedure They were able to raise the blood volume to normal levels by treatment with estrogenic substance in all patients whose initial blood volume was low. The same workers, by intraperitoneal injections of an extract from 60 per cent denicotinized tobacco, were able to produce gangrene in 33 of 48 male rats but in none of 12 female rats. McGrath

chill Both ul-

tion and rest pain returned. Tissue extract 568 (Sharp & Dohme), cc. three times a week, was given intramuscularly and after five injections the patient continued to have claudication but no rest pain Heart muscle extract (specially prepared and supplied by Eli Lilly), 4 cc intramuscularly, was then given three times a week, and after nine injections she was able to walk 15 blocks without developing claudication. Twenty-six more injections were given, and she was discharged from

TABLE 6—HOT WATER IMMERSION TEST*

TIME, P M	RIGHT FOOT				LEFT FOOT				ROOM TEMP
	1st Toe	3d Toe	5th Toe	Dorsum	1st Toe	3d Toe	5th Toe	Dorsum	
1 00	Admitted for temperature stabilization								
2:00	32 0	32 6	32 5	33 3	28 9	30 1	29 2	30 3	26 6
2 29	31 1	32 0	31 3	32.5	30 6	28 9	28 9	31 3	19 1
	Arms submerged in water at 45 C.								
2 30	31 5	31 6	31 5	32 9	31 5	29 5	29.3	31 6	22 6
2 35	33 0	31.4	30 7	32 6	31.2	30 3	29 6	31 4	24 0
2 50	32 4	33.3	32 8	33 3	31 4	30 5	29 2	31 5	21 0
3 05	33 0	33 3	33 0	33 0	31 8	30 5	29 3	32 0	25 4

* Temperature readings in centigrade Described by Landis

the clinic No conclusions are drawn regarding any specific effect of the tissue extracts which were used experimentally.

For several years the patient remained symptom-free, but she began to smoke again and for the past eight years has rarely been without symptoms or open lesions Thus far she has escaped a major amputation. She still smokes intermittently despite warnings, threats and cajoling. Meanwhile she has entered the age period in which arteriosclerosis obliterans may begin to play a complicating part.

The following factors were considered in arriving at the diagnosis of thromboangiitis obliterans (1) The patient is a Jewess; this is probably not very important but is mentioned as a point of interest. (2) She was 45 years old when symptoms first appeared. (3) There was no evidence of calcification in x-ray films of the affected extremities, taken for special study in that regard (4) Diabetes mellitus was not present. (5) She had smoked from eight to 30 cigarets a day for 37 years (6) Rye bread had been an important part of her diet since infancy and much of her life was spent in eastern Europe (where rye is often contaminated by ergot, although ergotism seemed unlikely here). (7) The pain was the

giitis obliterans into five groups according to occupation showed 23 men in sedentary occupations without exposure, 38 men doing manual labor without exposure, 20 men doing light labor with occasional exposure to cold, 17 men doing hard labor with occasional exposure, and 11 men doing hard labor with constant exposure to cold and wetness.

On the other hand, trauma often causes the original open lesion and is a common aggravating factor Numerous patients have been seen in whom, after an injury to a toe or a foot that failed to heal normally, it was discovered that extensive vascular disease existed and in some that it had existed before the injury. In these the available circulation had been adequate to maintain the life of the tissues under ordinary conditions but was not sufficient to promote healing following injury or to combat infection Among the innumerable types of trauma likely to initiate the process are unwise chiropody, burns, stubbing of the toes, chafing of the feet, frostbite and, especially in industry, the dropping of heavy objects on the toes or feet The last has become an important problem in compensation insurance cases, since once these patients are incapacitated they may remain so over long periods unless especially well treated It should be remembered that, because of the markedly impaired circulation, frostbite can occur in involved extremities on exposure to higher temperature than in normal extremities

Fungus infections may be an aggravating factor since the ulcers of thromboangiitis obliterans frequently occur between the toes, where moisture makes for ease of ulcer production and difficulty in healing

Race —Race should be mentioned largely to rectify the original misconception which arose because much of the early work was done in institutions whose patients were predominantly Jewish The condition has since been reported in Swedes, Chinese, Japanese, Koreans, Turks and Negroes In our clinic it has been seen in Irish, Germans, Italians, Negroes and people of many other

induced gangrene simulating that of thromboangiitis obliterans in the tails of albino rats by injecting ergotamine tartrate Female rats could be protected against this lesion by means of estrone, whereas male rats could not. Further studies of a similar nature may tell us why sex appears to be so important in thromboangiitis obliterans.

Ergot—The possibility that ergot is an etiologic factor in thromboangiitis obliterans has long been considered. A large number of the first cases to be recognized were in Jews from eastern Europe, where ergot is an endemic parasite on rye. Black rye bread was part of their daily diet. Epidemics of ergotism of two types, gangrenous and convulsive, had repeatedly been noted The inference was obvious but not necessarily correct.

Repeated experiments have demonstrated that ergot can produce a gangrenous condition in mammals and birds that clinically or pathologically is not unlike that of thromboangiitis obliterans Gangrenous conditions have also followed the clinical use of ergotamine tartrate and other ergot preparations in man. The clinical course of gangrene caused by ergot is apt to be more acute than that of thromboangiitis obliterans. After withdrawal of ergot, progress of the disease is usually halted and often improvement is rather rapid. For further discussion see Chapter V.

Today only a small percentage of our patients eat appreciable quantities of rye bread (practically none of which is made with ergot-contaminated rye), so we must conclude that, although ergot poisoning produces an occasional case of gangrene which at certain stages may resemble thromboangiitis obliterans, ergot is probably not a major etiologic factor in that disease.

Trauma; cold—Study of occupation and exposure to cold and water has failed to reveal a definite causal relationship with thromboangiitis obliterans. Ratschow studied a large group of men and women in the fishing industry, in which exposure to cold and water is excessive, and found that there had not been a single case in four years. Division of all of his patients with thromboan

tive skin reactions to rickettsia However, the rarity of typhus in the history of patients in other clinics makes the significance of his findings questionable This theory has been discarded.

Other suggested etiologic factors and disease processes include a prediabetic condition, increased viscosity of the blood, glandular dysfunction, high salt diet, electric shock, nutritional disturbances and polycythemia vera The meager evidence to support these suggestions does not warrant discussion here

Age—Age does play a part in determining the onset of the disease By far the greatest majority of cases begin between the ages of 21 and 45. Rare cases have been reported in persons under 15 and over 55, but in the older group one must suspect confusion with arteriosclerosis or a combination of the two conditions. It should be clearly understood that we are concerned here with the age of onset. Many patients in whom thromboangiitis obliterans began before they were 45 have lived into the age group for development of arteriosclerosis and have had exacerbations as a result of the combination of the conditions. It is possible that, instead of the female's having protective endocrine secretions, as has been generally accepted, the male during his actively potent years has a secretion which renders him susceptible to the condition and with the onset of the male climacteric the substance no longer is formed, thus preventing the onset of the disease in later life

Pathology

There are two important facts regarding thromboangiitis obliterans that are just now being accepted. First, it is a disease involving the arteries, veins and nerves and is not confined to the arteries alone Second, it is a generalized disease involving, on occasion, any or all of the vessels of the body, not necessarily being limited to the extremities. Buerger noted this long ago, mentioning in his monograph the involvement of spermatic arteries and veins and of the gastric artery in a case of ulcer of the stomach. Since then

national and racial groups. It is likely that in any racial group studied, especially if tobacco were widely used, the disease would be found.

Infection.—The inflammatory appearance of the lesions of thromboangiitis obliterans has led many workers to seek a bacterial cause for the disease Although organisms which were not considered contaminants have been repeatedly described, none have been established as causative agents. Syphilis has been practically eliminated as a possibility, notably because of the rarity of positive serologic evidence of syphilis in series of thromboangiitis obliterans patients and the converse rarity of thromboangiitis obliterans in series of syphilitic patients. The differential diagnosis may occasionally require thought.

A case of unusual interest in this regard is that of a man, aged 54, with a large moist ulcer involving the bases of the fourth and fifth toes on the left foot. Another ulcer was present in the right groin. A surgeon diagnosed thromboangiitis obliterans and recommended amputation of both legs However, examination revealed pulsation of both dorsalis pedis and posterior tibial arteries, which would be rare in thromboangiitis obliterans with such advanced lesions. The Wassermann reaction was 4 plus, the lesions were gummas and prompt healing followed the administration of arsenic and mercury. The ironic ending to this story rests in the fact that for the next eight years the patient walked to and from his business past the office of the doctor who had told him his legs must be amputated. He finally died of a cerebral accident.

A most interesting case was that reported by Allen and Lauderdale of accidental transmission of thromboangiitis obliterans from a patient to the operating surgeon as a result of the piercing of the palmar flesh by a spicule of bone from an involved toe So far as I can ascertain this is the only such instance on record We have been unable to duplicate this condition by transplanting involved bone into cats and rabbits

Numerous other diseases have been suspected but with insufficient proof to warrant serious consideration. One is typhus fever, as reported by Goodman, who noted a high incidence of posi-

tive skin reactions to rickettsia. However, the rarity of typhus in the history of patients in other clinics makes the significance of his findings questionable. This theory has been discarded

Other suggested etiologic factors and disease processes include a prediabetic condition, increased viscosity of the blood, glandular dysfunction, high salt diet, electric shock, nutritional disturbances and polycythemia vera. The meager evidence to support these suggestions does not warrant discussion here.

Age—Age does play a part in determining the onset of the disease By far the greatest majority of cases begin between the ages of 21 and 45 Rare cases have been reported in persons under 15 and over 55, but in the older group one must suspect confusion with arteriosclerosis or a combination of the two conditions. It should be clearly understood that we are concerned here with the *age of onset. Many patients in whom thromboangiitis obliterans* began before they were 45 have lived into the age group for development of arteriosclerosis and have had exacerbations as a result of the combination of the conditions It is possible that, instead of the female's having protective endocrine secretions, as has been generally accepted, the male during his actively potent years has a secretion which renders him susceptible to the condition and with the onset of the male climacteric the substance no longer is formed, thus preventing the onset of the disease in later life

Pathology

There are two important facts regarding thromboangiitis obliterans that are just now being accepted First, it is a disease involving the arteries, veins and nerves and is not confined to the arteries alone Second, it is a generalized disease involving, on occasion, any or all of the vessels of the body, not necessarily being limited to the extremities. Buerger noted this long ago, mentioning in his monograph the involvement of spermatic arteries and veins and of the gastric artery in a case of ulcer of the stomach Since then

numerous workers have reported pathologic evidence of involvement of the aorta and the blood vessels of the brain, heart, kidneys, liver, spleen, stomach, lungs and intestines.

Vascular lesions found elsewhere than in the extremities are not always completely characteristic of thromboangiitis obliterans, but it appears that thromboangiitis obliterans in the vascular tree is associated with a predilection for various types of blood vessel involvement such as thromboses, early sclerosis, etc. In general, the order of involvement appears to be from the extreme periphery of the vessels centrally toward the larger trunks, with occlusion tending to progress in the same order, but exceptions are noted.

The appearance of the vessels depends on the stage of involvement of the particular section of the vessel studied. The artery, vein and nerve are apt to be bound together so tightly that at times they cannot be completely separated It has even been suggested that the disease should be called neuroangiitis obliterans because of the involvement of the sympathetic nerves, especially the fibers in the adventitia which degenerate as a result of the inflammatory process and fibrosis. If in examination of the vessel proceeding distally a soft red thrombus is first encountered, the disease has been recently progressive. Peripheral to this is a grayish or brownish-yellow mass It can usually be differentiated from the wall of the vessel. Old thrombi are frequently pierced by fine canals which may exude small amounts of blood on squeezing. Unless the process is active locally, the bright red thrombus is not present The vessels are not characterized by either the crescentic or semilunar plaques or the brittleness typical of arteriosclerosis, but rather give the impression of induration with fibrotic changes. The veins are characteristically as liable to occlusion as the arteries and in some cases are even more extensively involved. *Thrombophlebitis commonly accompanies thromboangiitis obliterans and often symptomatically precedes it.*

Arteries —One of the earliest microscopic changes noted is the

presence of lymphocytes in and around the adventitia of small vessels Coincidentally, changes occur in the intima of the vasa vasorum The endothelial cells begin to proliferate, the nuclei become larger, and connective tissue density increases with fibrosis between artery, vein and nerve Polymorphonuclear cells are rare in the adventitia even when present in the media. Older lesions may show definite increase in the size of the blood vessels of the adventitia—evidently an attempt at collateral circulation. The media may contain many polymorphonuclear cells as well as lymphocytes Early in the process giant cell foci may develop which contain giant and endothelioid cells and broken down leukocytes. These foci are later replaced by connective tissue and disappear. Small vessels, usually not noted except by special methods of study such as those of Winternitz, become enlarged and dilated—another endeavor to increase the collateral circulation The muscle cells in general show remarkable resistance to change, only late in the disease showing marked interstitial fibrosis and atrophy. The interstitial tissue may be made up of mature connective tissue cells or young fibroblasts The changes are exudative and proliferative for the most part, atrophy occurring from disuse after occlusion of the vessel

Most observers have described active proliferation of the intima in thromboangiitis obliterans in both the veins and arteries It is greater than normal for the corresponding age (20–40) and is highly cellular The cells often have large oval prominent nuclei This proliferation of the intima probably does not in itself progress to the production of complete occlusion, rather it is probable that the same stimulus which initiates this process also precipitates the thrombosis which brings about the final step in total occlusion of the vessel Jager was able to demonstrate a general intimal reaction extending far beyond the site of the active lesions which he considered the fundamental initial ones. It consists of a cushioning of the intima with the development of nodular raised areas, with exudative and proliferative giant cells. He stated that in the large

arteries thromboangiitis obliterans resembles rheumatic fever, in the medium sized arteries, vegetative endocarditis, and in the small arteries, periarteritis nodosa Lymphocytes, polymorphonuclear cells and giant cell foci all commonly infiltrate the intima In the thickened intima concentric layers of elastic tissue are found frequently but not invariably The tissue is not split and distorted as in arteriosclerosis, but is frequently increased.

Although the inflammation involving the arteries is sometimes acute, it is usually of chronic nature.

After the thrombus is well organized, cells of a fibroblastic type grow in toward the center of the clot where they form a network of sinusoids Some autolysis takes place centrally, but within the sinusoids well preserved erythrocytes may be found. Absence of fibrin within the sinusoids suggests that the cells circulate freely therein Mahorner has questioned whether the cells which line these spaces have grown from endothelium. They appear to penetrate the thrombus singly and have the characteristics of young fibroblasts but are capable of metamorphosis to line the blood channels. This process is not completely understood.

The end-stage of the process is, however, quite well agreed upon. There is a marked increase in connective tissue in the adventitia and surrounding area. This perivascular fibrosis is composed of closely packed mature cells binding the artery, vein and nerve closely together. The vasa vasorum are enlarged, with intimal hyperplasia Lymphocytes are still common, but in most sections polymorphonuclear cells are also found throughout.

The media becomes infiltrated by connective tissue and small blood channels, but the muscle cells remain fairly well preserved The thrombotic mass occluding the lumen is canalized by blood vessels with three coats It has become changed to a mass of fibroblasts and lymphocytes.

Veins.—The process in the veins is not vastly different from that in the arteries. According to Lindenbaum and Kapitza, in the first stage one finds a fresh thrombus with an inflammatory

reaction in the wall, perivascular edema and leukocytic cellular infiltration. Small granulomatous nodules begin to appear in which necrotic foci develop. Organization then takes place. Buerger pointed out years ago that the foci of giant cells which develop resemble those seen in tuberculosis. The thrombus is infiltrated by lymphocytes and histiocytes. The process goes on to obliteration of the lumen with or without canalization In some veins no thrombus is found, only a thickening of the intima encroaching on the lumen

Nerves—The changes in the nerves are inconstant and appear to be due to pressure and ischemia secondary to the great overgrowth of connective tissue of the neurovascular sheaths The nerve changes do not precede changes in the accompanying blood vessels; they are greatest at the points where the vessels are most involved and where ischemia is most severe. In the most peripheral nerves striking degenerative changes are noted Lymphocytic infiltration, thickening of the perineurium, absorption of myelin and an increase in the number of nuclei of the sheath of Schwann are observed, but these changes are probably the result of long-sustained ischemia since they also occur in arteriosclerosis

Signs and Symptoms

Although the disease may be present for an indeterminate period without serious symptoms, most patients probably experience minor local sensations early in the course without recognizing their importance Detailed questioning of a number of patients has confirmed this belief. The early, frequently unreported symptoms consist in the feeling of pins and needles, formication, coldness or a burning discomfort in the area in which the earliest disturbances of circulation are occurring

PAIN

The presenting symptom is usually pain, which may be of one or several types Goldsmith and Brown carefully analyzed the

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types of pain experienced by 100 consecutive patients with thromboangiitis obliterans. The pain may be the result of one or more of three factors: (1) that arising from the blood vessels themselves, (2) that due to ischemia of tissues, including nerves, and (3) that attributable to secondary infection. Pain may also be classified as that *related to exercise* and that which occurs *with rest.*

Intermittent claudication—This exemplifies the pain related to exercise. It is the symptom which most often brings the patient with thromboangiitis obliterans to the doctor, being the initial complaint of about 75 per cent of patients. Typically it is a pain in the muscles of the extremity after a given amount of exercise. The patient usually can walk a certain number of blocks, then pain forces him to stop After a few minutes of rest he is able to go on again and can usually walk an almost identical distance before pain halts him. The pain most commonly occurs in the muscles of the arches, calves or thighs and is characterized by a dull aching fatigue or a sense of cramplike constriction in the affected muscles. The severity of the claudication is frequently increased by cold weather and is also made more severe by walking rapidly or uphill.

As the disease advances, with blockage of the larger vessels, the areas of claudication pain ascend the leg until the thigh is involved and the vessels of that area are found to be occluded. It should be noted that the major trunks may be patent, whereas some of the branches supplying important groups of muscles may be occluded. An example is the presence of intermittent claudication of the muscles of the thigh or calf while the dorsalis pedis and posterior tibial vessels are palpable and oscillometric readings are within normal limits.

The pain must be differentiated at times from rheumatic and arthritic pain. In addition to testing for vascular or joint damage we have found it helpful to question the patient as to whether he must sit down to obtain relief. When the pathologic process

is in the joint, the patient usually has to take his weight off the joint to obtain relief, whereas the pain due to true claudication (ischemia) is relieved merely by cessation of active exercise of the muscles. This seems logical in the light of our present understanding of the cause of claudication pain. It is apparently due to a chemical substance accumulated during muscular contraction when blood supply is deficient The syndrome is readily reproduced in a normal limb when a tourniquet is bound tightly enough around it to occlude the arterial blood supply and exercise is undertaken. Roth has shown that the lactic acid in the veins of the affected extremity increases sharply after exercise by patients with occlusive vascular disease, but the increase is not consistently parallel with the intensity of the pain

Claudication pains in the calves usually indicate occlusion of the popliteal arteries, but we have seen a number of patients with typical claudication pain in the calves in whom the major vessels were open down to and including the dorsalis pedis and posterior-tibial arteries The impression that this indicates involvement of branches supplying groups of calf muscles has been verified by arteriographic studies This particular phenomenon has been noted more commonly in arteriosclerotic patients than in patients with thromboangiitis obliterans.

Rest pain (pain occurring during rest) —Pretrophic pain may occur before the appearance of ulceration or gangrene, but one or the other usually develops at the site unless treatment or spontaneous improvement in circulation checks the progress of the condition. The pain is described as a burning, gnawing type, worse at night, or as an aching sensation associated with local tenderness, probably due to ischemia of the tissues and nerves supplying the area The patient not infrequently obtains some relief by walking around the room or by hanging the foot out from under the bed covers

Pain with ulcers or gangrene —Formerly more than 50 per cent of the patients we saw with this disease had ulcers or gangrene with

pain. Today, as a result of more widespread knowledge of the disease, the condition is diagnosed in the early stages before there is any necrosis of tissue. In general, the more advanced the ulcer or gangrene, the more severe the pain. This pain is characterized as excruciating, burning, stinging, lancinating, aching It is usually continuous but may be paroxysmal. It is often relieved by dependency and is made worse by overheating—a problem discussed later in this chapter under treatment. It is often worse at night when metabolic processes and blood pressure are lowered and the patient's attention is not diverted from the lesion Hyperparesthesia around the lesion is common.

This pain usually develops with the opening of the ulcer or gangrene, which often occurs months or years after the onset of the disease, although it may be encountered at the site of a future ulcer as the symptom for which the patient first comes for medical care Ordinarily it persists until the lesion is completely healed and sometimes continues for weeks thereafter.

Pain due to inflammation of blood vessels.—Phlebitis is common in thromboangiitis obliterans. (It is discussed in greater detail later in the chapter.) This complication is a true component of the clinical and pathologic syndrome. The pain of phlebitis is typical of all phlebitis—a dull, aching or burning type with local tenderness over the vein, stiffness or soreness of nearby muscles, characteristically aggravated by exercise. The pain of the arteritis is only slightly more severe than that of the phlebitis. The arteritis starts as a tender nodular swelling and progresses along an artery, which becomes enlarged and pulseless. A generalized aching pain develops, with coldness peripheral to the involved arterial segment. Involvement of the nerve supply to the vessel walls probably accounts for the pain

Pain of sudden occlusion.—The occurrence of sudden occlusion in thromboangiitis obliterans has been emphasized by Buerger and many other writers. The occlusion is recognized by the onset of a sudden sharp pain in the foot or hand of the involved extremity.

The pain is projected peripherally and is frequently accompanied by cramping pain in the muscles. The extremity becomes cold, clammy, numb and pale or cyanotic. The pain usually subsides

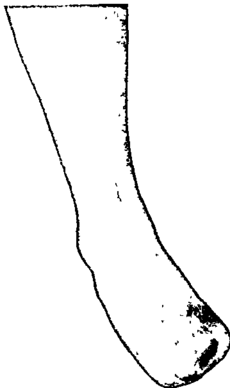


Fig. 45—Scars of nerve section in healed and arrested case of thromboangiitis obliterans. Only partial relief of pain was obtained by nerve section.

gradually and practically disappears in 48–72 hours. Movement or pressure may cause return or aggravation of the pain, which is probably due to ischemia of mixed nerves and to severe vasospasm. If the condition is not progressive the temperature of the extremity rises slowly, returning to normal as the pain recedes. This is most likely due to the rapid increase of collateral circula-

tion by release of spasm in the vessels Residual hyperesthesia, numbness, tingling, paroxysms of pain and claudication may be present for weeks

This is the history in cases in which there is at least a fair degree of recovery, but it should be understood that this complication is most serious. Kvale and Allen reported that about 66 per cent of limbs so involved require amputation. This high percentage over that found with sudden occlusion not associated with vascular disease, as by emboli, is readily explained by the previous severe impairment of the arterial blood supply in most cases and the resulting inability of the tissues to survive an additional diminution in blood supply. This event is apt to occur in the more rapidly progressive type of thromboangiitis obliterans

Ischemic neuritis.—This usually develops rather late in the course of thromboangiitis obliterans. The pain may be sharp or dull or shooting, pulling, tearing and agonizing. It involves extensive areas which do not necessarily correspond to any definite distribution of nerves. It may be paroxysmal or constant. The pain may be so severe and protracted that nerve section (Fig 45) or rarely amputation is required It is due to ischemia of the nerve with degenerative changes or to actual inflammation from contiguity of diseased vessels

Vasospastic pain.—Spasm of the arteries that responds to vasodilators such as nitroglycerin usually produces blanching or cyanosis without true pain, but occasionally cramplike pain is present

Unclassified pain—Not infrequently it is difficult to analyze the pain of which the patient complains. Often several types of pain are present that the patient cannot clearly separate. At other times the cause is deep in the muscles and results in vague discomfort which may be attributable to any of several factors

TEMPERATURE CHANGES

The complaint of coldness in the extremity, especially the peripheral third of the limb, seems paradoxical in view of the presence

of "burning" pain. Yet both are sometimes found in the same extremity and occasionally at the same time. More often, however, the coldness is complained of when the affected part is exposed to room temperature or to cold, whereas the burning pain is most pronounced when the foot is warmed, as under the bedclothes or by artificial heat, and especially with overheating. Control of this factor is discussed under treatment

COLOR CHANGES

The patient usually notices the marked rubor which later becomes cyanosis when the extremity is dependent, but does not often discover the marked pallor which occurs on elevation This syndrome is not specific for thromboangiitis obliterans, occurring whenever circulation in the major arteries of a limb is defective The striking rubor in the presence of deficient circulation is produced by several mechanisms, individually or collectively (1) If the skin is moderately cold (50 F or thereabouts), the free exchange of oxygen is interfered with and the blood remains bright red (2) The minute vessels are damaged and dilate, thus containing more than the usual amount of the bright red blood (3) The dilatation is compensatory, serving a useful purpose in supplying maximal amounts of blood to tissues in which the total blood supply is low.

Not infrequently the rubor is gradually converted to cyanosis, especially when the foot is dependent for some time It may develop in slowly spreading patches The explanation for this type of cyanosis seems to rest on the fact that the oxygen of the blood is gradually taken up by the tissues during prolonged stasis. The stasis may be due to arterial damage which prevents sufficient propelling force to move the blood along and to venous damage which may prevent proper drainage of the blood supply. Thrombosis of the artery supplying a digit may cause pale cyanosis of that digit; the cyanotic area may be more extensive if larger vessels are involved.

On elevation above the heart level the extremity becomes pale as the blood drains out by gravity and new blood does not flow in at an equal rate. This observation has been used as a test for deep vessel occlusion (Buerger). In a normal person lying supine the normal color of the foot is maintained on elevation to 180 degrees; slight reddening occurs on dependency of 60 degrees or less. In the presence of arterial obstruction abnormal pallor is present on elevation and abnormal rubor on dependency. The appearance of pallor can be hastened by stroking the skin centrally or by having the patient move the toes actively. Both the pallor and the rubor may be patchy at first owing to differences in the rate at which various areas are drained or supplied with blood from the damaged circulatory tree. Rubor of this type can thus be differentiated from that of infection, since the latter does not disappear on elevation.

Typical rubor in the toes should be interpreted as significant of circulatory impairment even when the major supplying artery (for example, the dorsalis pedis) is palpable. The damage may be peripheral to the point of palpation. When impaired circulation is complicated by infection, which is not uncommon, the local area remains red during elevation while the rest of the surrounding tissue pales visibly. After a few minutes of elevation small wrinkles often appear in the skin as edema decreases.

EDEMA

Edema is very common in thromboangiitis obliterans. It is due primarily to imbalance of the capillary-tissue fluid interchange rather than to lymphatic damage. The edema may be based on at least three different factors or may be due to a combination of influences. (1) Obstruction of the deep veins secondary to phlebitis results in a damming back of the blood and marked increase in intercapillary pressure, producing an outpouring of fluid into the surrounding tissues. (2) As a result of long-continued inactivity and dependency of the extremity, gradually

accumulating intercapillary pressure becomes a principal factor, with toxic products probably injuring the capillary walls and producing permeability. (3) The edema of inflammation, which is secondary to toxic injury to the capillary walls, increases permeability

PHLEBITIS

Phlebitis, either superficial or deep, or both, occurs in about 50 per cent of cases of thromboangiitis obliterans. It should not be forgotten that it is frequently the presenting syndrome, often masking the arterial involvement for a time Idiopathic recurring phlebitis in a young male is an indication for thorough consideration of the possibility of thromboangiitis obliterans This usually occurs in the lower extremities, most commonly below the knee. Evidence of inflammation is noted along the course of the involved vein in the form of tenderness, redness and swelling There may be nodules along the vessel—tender, red, circular areas which sometimes coincide with the localization of the valves. The process in any given area may last six weeks or more before subsiding, only to appear at another site. This may be responsible for edema

TROPHIC CHANGES—FISSURES, ULCERS

Prolonged diminution of blood supply results in cutaneous changes. The skin becomes tense and shiny or dry, scaly and pigmented. The nails show trophic changes, with thickening, discoloration, ridging and failure to grow Sometimes no growth is apparent for months Tissue in this state has extremely poor resistance to any kind of injury or infection so that ulcers or fissures develop with the slightest trauma. Dropping an object on a foot, kicking or stubbing the toe, paring a corn or callus too closely or a minor operation such as the trimming or removal of an ingrown nail may precipitate serious ulceration resulting in loss of a toe

or the whole foot (Fig. 46). The problem of trauma is assuming increasing importance in accident and compensation insurance Infections, bacterial or fungus, are frequent precipitating causes of deep fissures between the toes

The ulcers and fissures are characteristically rather deep, sharply



Fig 46—Huge ulcer over inner malleolus following injury at this site in a patient with thromboangiitis obliterans.

defined, moist, purulent, inflamed, exquisitely tender and excruciatingly painful. They are extremely slow to heal unless active, proper treatment is instituted

GANGRENE

The ulcers and fissures just described may progress superficially or undermine the digits until they are completely gangrenous. The process often spreads until all digits and even the hand or foot is






[illegible]

involved (Fig 47). With occlusion of the major blood supply to the area more or less massive gangrene may occur. This fortunately has become rare since proper precautions and treatment may arrest the disease in its early stages.

Massive gangrene is usually moist, and soft necrosis sets in. The skin and subcutaneous tissues disappear, so that frequently the tendons and bones are clearly seen. Spontaneous amputation may occur, formerly more than one extremity, and sometimes all four, were serially involved, but with modern treatment this is most unusual Simultaneous acute ulceration in all four extremities is extremely rare, the only case reported up to 1946 having been from our clinic (Fig 48). The pain of this gangrene is excruciating—one of the severest types of pain known to medical practice

Diagnostic Procedures

One should never forget that thromboangiitis obliterans is potentially a disease involving any and all blood vessels in the body. Electrocardiographic studies should be made in each case, and one should constantly keep in mind the fact that complaints referred to the abdomen, chest or head may be related to the disease being treated in the toe I have seen patients with involvement of the coronary, mesenteric, splenic and cerebral arteries, and this is the experience of many students of the disease Enumeration of all of the possible symptoms would be impossible, but alertness on the part of the physician to the possibility of unusual localization is vital The symptoms naturally depend on the organ involved

Search for pulsation.—Absence of pulsation in peripheral vessels that normally are pulsating is common in thromboangiitis obliterans. During every physical examination which pretends to be complete, the vessels listed below should be palpated routinely, since occlusion is always serious and early recognition may avert disaster The order of frequency of closure of palpable arteries by thromboangiitis obliterans is:

Lower extremities
1. Dorsalis pedis artery
2. Posterior tibial artery
3. Popliteal artery
4. Femoral artery

Upper extremities
1. Ulnar artery
2. Radial artery
3. Brachial artery

Head and neck
Temporal artery

when none are present. Vessels may be aberrant and so placed

Oscillometric readings.—Oscillometric readings are exceedingly helpful in determining the level of closure of the major vessels of an extremity Physicians are constantly coming to erroneous conclusions regarding the presence of patent vessels because prominent pulsations of their finger-tips suggest normal pulsations that palpation is difficult or impossible, yet provide a perfectly adequate blood supply Without an oscillometer it is impossible to determine the location of an occlusion between the ankle and the knee or the knee and the groin unless arteriographic study (a much more involved procedure) is undertaken Absence of pulsation is highly significant and warrants exhaustive study

Allen test.—For the determination of patency of the ulnar artery, which frequently is not palpable, Allen's test has considerable value (For details, see Chapter II) In rare instances the ulnar artery is congenitally absent This condition is frequently bilateral, and ulnar function has been assumed by the radial or interosseous arteries

Arteriographic studies.—These probably give the most complete picture obtainable of the state of the circulation of the major and the collateral vessels The procedure (pp. 60 ff) is, however, somewhat complicated and should be undertaken only by experienced persons. Also, the most satisfactory radiopaque medium, Thorotrast, is slowly radioactive, which makes its use objectionable to some workers. Over 3,000 injections of which I have knowledge

have nevertheless been given in eight years without proved deleterious effects Diodrast is more widely used by radiologists but in my experience and knowledge reactions to it are more common and more serious than to Thorotrast. This includes death. Whichever one elects, its use should be reserved for situations in which the knowledge it supplies is essential to the care of the patient

Reflex vasodilatation.—The degree of potential vasodilatation has been determined in many of our cases by the method described by Landis and Gibbons

If the feet are being studied, the arms are immersed in hot water at 43 C (109 4 F.) for 45 minutes. Normally the temperature of the toes rises to 32 5 C (90 5 F.) or above in less than 20 minutes, but because in some instances response is delayed, 45 minutes is a safer period When there is occlusive arterial disease the temperature does not rise or does not reach the normal level. The procedure is reversed if it is desired to test the hands

The test can be modified by the application of blankets and hot water bottles to the body or a heating pad to the abdomen. This is not an infallible test and should be checked by use of lumbar *sympathetic block or spinal anesthesia* if the results seem doubtful

Differential Diagnosis

*Raynaud's disease.**—The differentiation of thromboangiitis obliterans and Raynaud's disease rests on the following points

1 Ninety-eight per cent of cases of thromboangiitis obliterans occur in males, whereas 70 per cent of cases of Raynaud's disease are in females

2. Thromboangiitis obliterans produces occlusion of the vessels so that in most cases some of the normally palpable vessels are pulseless. Oscillometric readings show absence or diminution of pulsation. In Raynaud's disease the normally palpable vessels are occluded only in extremely advanced stages. At room temperature

* See Chapter VI for discussion of the difference between Raynaud's disease and the Raynaud syndrome.

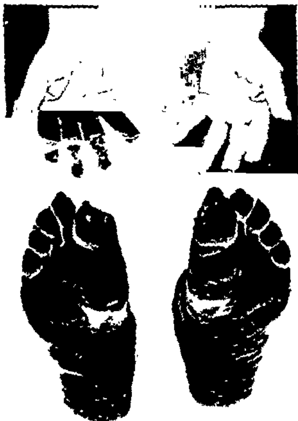


Fig. 49.—Advanced thromboangiitis obliterans, showing involvement of all extremities.

or above, all vessels are pulsating. Oscillometric readings are normal. In extreme cold there may be temporary spasm of the vessels, but when the extremity is warmed pulsation returns to normal. In certain cases of thromboangiitis obliterans Raynaud's syndrome appears early in the course and, in the absence of organic occlusion, may be difficult to differentiate, although it is frequently asymmetrical and may involve only one or two digits In the presence of occluded vessels the diagnosis remains thromboangiitis obliterans unless, as previously mentioned, occlusion occurs late with a dominant Raynaud syndrome.

3. In thromboangiitis obliterans evidence of occlusive vascular disease is present, with rubor on dependency, pallor on elevation and intermittent claudication or extreme fatigue on exercise. In Raynaud's disease none of these manifestations are present. Pallor (blanching) does occur on exposure to cold, or with emotional excitement, with marked rubor (erythema) on return to warmth or emotional equilibrium.

4 Thromboangiitis obliterans is usually asymmetrical as far as the acute lesion is concerned Raynaud's disease is usually bilateral and often quadrilateral

5 The ulcers of thromboangiitis obliterans are usually moist, deep and inflamed and tend to invade the surrounding tissues Massive gangrene is common in untreated cases The ulcers of Raynaud's disease are usually superficial, involving the tips of the digits. Massive gangrene is rare as the disease is encountered today Ulcers of both diseases are excruciatingly tender.

6. Phlebitis and edema are very common in thromboangiitis obliterans. In Raynaud's disease their occurrence is entirely coincidental.

7. The skin in thromboangiitis obliterans becomes atrophic, thin and reddened, and the nails may cease growing for months at a time. The skin in Raynaud's disease often becomes sclerodermatous and there may be some atrophy of the subcutaneous tissues Nail growth may be retarded, but in my experience unless

scleroderma is advanced this is not as pronounced as in thromboangiitis obliterans.

8 In thromboangiitis obliterans pain is a dominant symptom on activity or at rest, with or without ulcers. In Raynaud's disease pain is seldom important unless ulcers are present.

9. Arteriographic studies in cases of thromboangiitis obliterans show definite blockage and moth-eaten appearance of the arteries, especially toward the periphery. Arteriographic studies in Raynaud's disease not in spasm show normal findings.

10. Capillary microscopy of the affected area in thromboangiitis obliterans shows some decrease in the number of visible capillaries, the rate of blood flow is slow and there is frequent stoppage. The capillaries are slightly dilated throughout. Some cases show a striking vasoconstrictive phenomenon. When the area is cool only a few capillaries may be seen in each field and these are constricted. When warmed a few more capillaries will open The blood flow is jerky, probably owing to the opening and closing of a precapillary arteriole allowing small spurts of blood to pass through. The capillaries in Raynaud's disease show enormous dilatation of the venous limb and relative dilatation of the arterial limb. This change is not found in all of the capillaries but involves a larger percentage of them as the disease becomes more severe and of longer standing In the stage of blanching few cells can be seen in the capillaries. They do not move appreciably until the arteriolar spasm relaxes

Arteriosclerosis.—1. Thromboangiitis obliterans is a young man's disease; arteriosclerosis is a disease of old persons of either sex. Practically all patients with thromboangiitis obliterans have initial symptoms before the age of 55 and most before 45. The initial symptoms of senile arteriosclerosis rarely appear before age 45 and in most instances not before 55. There are striking exceptions in both groups. When the two diseases are present simultaneously we sometimes have difficulty in evaluating the respective importance of the two conditions.

2 In thromboangiitis obliterans phlebitis and edema are common. In arteriosclerosis neither is present except coincidentally and they result from other causes

3 Ulcers of thromboangiitis obliterans are moist, deep, inflamed and excruciatingly painful and tender The ulcers of arteriosclerosis are dry, superficial and not as tender or painful. Exceptions are the ulcers of diabetes or infected ulcers, which are often purulent and inflamed. The ulcers of arteriosclerosis may be surprisingly painless in some cases. Massive gangrene may occur in either condition.

4 X-rays show no calcification in thromboangiitis obliterans Calcification is seen in the walls of the arteries and sometimes also of the veins in arteriosclerosis. Calcification does not necessarily imply occlusion because vessels may be patent throughout despite definite evidence of calcium deposits along the entire length of the walls On the other hand, one strategically placed and shaped plaque may produce thrombosis and occlusion of a major vessel. Cholesterol plaques may occlude vessels in arteriosclerosis without x-ray evidence of calcification

5 The retinal fundi are usually normal in thromboangiitis obliterans. The vessels may show silver wiring or other signs of sclerosis in arteriosclerotic patients

Emboli and thrombi.—The commonest forms are emboli from vegetations and mural thrombi in the heart lodging in a peripheral artery. They are sometimes difficult to differentiate from sudden occlusion in thromboangiitis obliterans, although usually there is definite evidence of the type of cardiac damage likely to throw off emboli, such as auricular fibrillation, vegetative endocarditis, mitral stenosis with ball thrombi and myocardial infarction with mural thrombi Emboli and thrombi may occur with or following surgery and severe infections such as pneumonia, typhoid fever and puerperal sepsis These usually present no difficulties in diagnosis. The same is true of emboli or thromboses following trauma.

Cervical rib.—This sometimes produces a confusing picture, but the signs always occur in the upper extremities, the typical rubor and gangrene of thromboangiitis obliterans are not present and cervical rib can be ruled out by x-ray of the cervical portion of the spine

Other shoulder girdle syndromes, including the *scalenus anticus, costoclavicular* and *hyperabduction syndromes,* must sometimes be considered. (See Chapter X.)

Other diseases.—Periarteritis nodosa, rheumatic and syphilitic arteritis, vascular anomalies, tumors of the blood vessels, diseases of the central nervous system and arthritis may be confused with thromboangiitis obliterans. A complete history and physical examination should easily eliminate most of them.

Course

The rate of progression of thromboangiitis obliterans varies greatly from case to case In some the course is exceedingly acute, with rapid spread to the various vessels, ulceration and gangrene of one or more extremities. In others it progresses slowly. The slowly progressive cases may extend into the older age group with development of superimposed arteriosclerosis. Occasionally when thromboangiitis obliterans has become quiescent with enough residual circulation for the continued life of the extremity, the development of critically placed arteriosclerotic plaques upsets the equilibrium, leading to vascular crises even including the precipitation of gangrene. Fortunately this type of episode is rare.

Treatment

A detailed discussion of all of the forms of treatment which have been proposed for thromboangiitis obliterans would fill this volume and be largely valueless. Our endeavor will be to discuss the methods which have stood the test of time and which we now use. Comments on other forms of therapy will be included when indicated In over 500 cases studied since 1931 the major

amputation* rate has been reduced from 70 to less than 5 per cent Numerous digits that were severely involved when first seen have been lost

MEDICAL MANAGEMENT

Rest.—Whenever there is ulceration, gangrene, conspicuous progressive discoloration, pronounced and sudden local coldness or severe rest pain the involved extremity should be placed at rest The level selected for the maintenance of the most satisfactory circulation possible in the circumstances has been shown by Reid to be exceedingly important If the extremity is kept too long in a dependent position the veins become engorged and there are increased venous and capillary pressure and stagnation of blood If, on the other hand, the extremity is kept elevated it becomes blanched and bloodless in appearance and the tissues become severely ischemic since the force in the diseased arteries is usually insufficient to carry fresh blood to the tips of the extremity. Such elevation, when prolonged, frequently led to amputation in the past

The most efficient level at which to obtain proper blood supply is that at which the superficial veins fill to the extent that they project slightly above the level of the skin *This is usually 3–6 in. below the position of the heart*. At this level gravity assists arterial blood flow into the limb and the return is not retarded by too greatly increased venous back pressure

Rest should be continued until the lesion is healed or the acute episode is completely past After this, activity should be undertaken guardedly and under observation until a return of the critical state is considered unlikely.

Care of the extremities.—Once the diagnosis of occlusive vascular disease is made, meticulous care must be taken of the hands

* By major amputation is meant the loss of a foot or hand or a greater proportion of any extremity

and feet. They should be washed carefully at least daily with warm, not hot, water and rubbed thoroughly afterward with olive oil or lanolin to keep the skin soft. Corns and calluses should be carefully softened with salicylic acid ointment; paring except by experts should be discouraged. The nails should be cleansed and pared with extreme care to avoid any minor surgical lesions Trauma and frostbite must be avoided in all possible ways. Shoes must be soft and fit well but of ample size Socks should be of soft wool to cushion the feet and prevent abrasion.

Dermatophytosis must be treated with great thoroughness In my experience the most satisfactory method has been the use of potassium permanganate solution (1:10,000) soaks every other day for 30 minutes at 94 F. (34 4 C.). Whitfield's ointment, half-strength, applied daily is also helpful; it should not be used on an open ulcer. The use of any ointment must be undertaken with caution and the area must be observed for any evidence of maceration. X-ray therapy is not recommended for patients with occlusive vascular disease. Sopronol (Wyeth) and Timofax (Burroughs Wellcome) powders and ointments have proved effective.

Abstinence from tobacco —The evidence that the use of tobacco is at least an aggravating, if not a truly etiologic, factor in thromboangiitis obliterans has already been presented. *Its use must be completely and permanently prohibited* if satisfactory therapeutic response is to be obtained. Good results are to be expected from the treatment outlined here provided the patient will stop smoking entirely.

Every patient who has suffered a major amputation in our series of more than 500 patients since 1931 has continued to smoke, often surreptitiously, even though warned many times of the dire consequences. Patients who steal an occasional smoke usually have ulcers which are slow to heal, continue to ooze and look inflamed If an ulcer has been healing satisfactorily and suddenly becomes inflamed and enlarges, careful questioning will usually elicit an admission of smoking, although at first denied. Numerous patients

whose disease has been quiescent from six months to several years have returned with a new ulcer and have admitted that they had smoked, followed in a few days or weeks by return of pain and ulcer. The rule must be *"Absolutely no smoking, now and forever!"*

Alcohol.—In beverage form alcohol, on the other hand, is a good vasodilating substance and for this reason should be used freely. During acute crises of pain with ulceration I give fairly large doses, ranging from 1½ oz. to the amount the patient can tolerate without undue excitement. It often has a striking sedative effect and sometimes seems as effective as morphine. After the acute stage has passed the patient should have two cocktails or highballs each evening to encourage vasodilatation of the remaining functioning vessels.

Papaverine.—This has been used as a vasodilator or for the release of smooth muscle spasm. Experience and certain experiments indicate that its action is less reliable than that of either alcohol or reflex heat, but it tends to relieve pain. The average dose of papaverine hydrochloride is ½ gr. (0.03 Gm.) orally or intravenously up to four times daily. The intra-arterial injection of the same dose of papaverine has recently been found to be more effective in the emergencies of sudden occlusion. For example, for occlusion of a popliteal artery, papaverine should be injected into the femoral artery. The dose is 1 gr. (0.06 Gm.) in 5 cc. of distilled water. This may be repeated several times at six hour intervals.

Codeine phosphate-acetylsalicylic acid, barbiturates, Demerol; methadon; morphine.—These all have some usefulness and should be given as indicated. Morphine should not be used except in extreme emergencies or for temporary uncontrollable pain, since these patients readily become addicts because of the chronicity of the disease.

Typhoid vaccine intravenously.—The value of nonspecific foreign protein therapy, first suggested by Goodman and Gottesman

in 1923 and used extensively by Brown, Allen and our group, has been definitely established. Typhoid H antigen (Lilly) and a typhoid vaccine prepared especially for this purpose by the Kirk Biological Laboratories are widely used.

The dilution of 100,000,000 typhoid bacilli per cc. permits accurate measurement of the dose Severe reactions may be caused by attempts to measure small doses of typhoid vaccine from a highly concentrated suspension. Suspensions tend to settle and vary in concentration unless thoroughly shaken. The risk is minimized by using low concentrations and shaking well before use. The routine used for treatment follows.

The first dose is 5,000,000 organisms. Injections are given every three days provided the effect of the previous dose has completely worn off The object is to obtain a 2–3 degree (F.) rise in oral or rectal temperature without a chill. Although there is usually a slight drop in surface temperature preceding the rise, this is inconsequential if no chill occurs. The surface temperature of the tips of normal extremities rises 4–6 degrees (F) with this amount of fever; in a diseased extremity the increase of surface temperature is affected by the degree of occlusion of the arterial supply to the limb, including the collateral vessels

When 5,000,000 organisms fail to produce satisfactory fever, the dose is increased to 8,000,000 or 10,000,000 organisms and kept at that level so long as the response is satisfactory. Increases of 3,000,000–5,000,000 organisms are made whenever the effects of the preceding dose are inadequate. If the temperature rises above 103 F. or a chill occurs, the next dose is decreased by 3,000,000–5,000,000 organisms. Doses of 200,000,000 and more have been given, but with most patients the peak seems to be 70,000,000–130,000,000, and this dosage can be continued indefinitely. By proceeding carefully in this manner, in over 12,000 injections we have had no serious untoward effects definitely attributable to the treatment. During acute infections or other serious illness the injections have been suspended. This treatment is usually continued for two or three months after complete healing of the ulcer

The results of this procedure have been highly gratifying, with relief of pain in small ulcers after the second or third injection and with rapid healing The major gangrenous processes naturally

respond more slowly, and there have been rare failures, but the results appear to be more satisfactory than after any other form of intravenous therapy. Typhoid vaccine has not seemed to affect the syndrome of intermittent claudication appreciably.

Adrenolytic, sympatholytic and ganglionic blocking drugs.—These drugs and their actions are discussed in the chapter on arteriosclerosis obliterans (p. 148) They have been tried extensively in the treatment of thromboangiitis obliterans Although their clinical value is not conclusively established, the evidence appears to warrant their further clinical trial

Priscoline, 25–50 mg. three to five times a day, is most commonly used today. When this dosage produces reactions that are too disturbing the dose may be reduced or taken during meals. Roniacol in similar doses is tolerated better by some patients

ACTH and cortisone.—Brief mention should be made of the experimental use of ACTH and cortisone in the treatment of thromboangiitis obliterans. The results in our experience are equivocal In a few patients the claudication distance has increased and the pain has decreased These results may be due to what has been termed the "analgesic effects" of these substances In a few patients the oscillometric readings have increased but their implications also are uncertain Pending further observation no final conclusions can be drawn They may be of help in some stubborn cases The dose of either substance has been 25 mg four times a day for one to two weeks, followed by reduction to twice or even once a day The usual contraindications to the administration of these substances holds in this disease.

Controlled heat.—Whether obtained by means of cautious application and careful observation or, preferably, by a thermostatically controlled foot cradle (pp 140 f), heat is sometimes valuable in reducing pain and establishing normal circulation. The correct temperature appears to be 31.1–35 C (88–95 F.) Too much heat increases the metabolic demands for a greater blood flow, rapidly depleting the available tissue nourishment, inasmuch as

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the arteries are blocked above the involved area this demand cannot be fulfilled, the deficit and hence the ischemia are increased and the tendency to gangrene is aggravated. Therefore *the local use of all types of high temperature heating equipment, including hot water bags, electric bulbs, infra-red lamps and diathermy, is contraindicated in vascular disease.* I have seen severe burns produced in more than 70 patients by ill-advised use of such equipment, four lost their legs as a result of the severe burns in tissues with very low resistance to infection and inability to diffuse the heat rapidly by adequate blood flow.

One patient died. An area 6 cm. in diameter had been broiled through his foot by the use of short wave with the electrodes on the dorsal and plantar surfaces The flesh literally necrosed, liquefied and disappeared, leaving a hole through the foot bridged by the metatarsal bones The mixed but predominantly steptococcus infection could not be controlled and despite amputation the patient died. This was before modern chemotherapy.

If high temperature heat sources are to be used at all, application should be made at a high level, preferably across the hips to encourage dilation of the major and collateral vessels from above downward.

Refrigeration.—Refrigeration should not be used to save limb with occlusive vascular disease because it causes spasm of th smaller vessels on which the life of the tissues depends and the accentuates the local ischemia. Refrigeration should be reserve for special cases in preparation for amputation; for this purpo it is suitable for elderly, diabetic, arteriosclerotic patients rath than for thromboangiitis obliterans patients in whom refrigeratic may induce vascular spasm in other extremities involved by th disease.

Wet dressings.—Because cool wet dressings chill, wet dressin should be used only when the temperature can be maintain between 33 and 35 C. (91.4 and 95 F.). This can be accomplish only by the use of a temperature controlled cradle and alm

constant attention by a nurse. Only the mildest of solutions, preferably normal saline or penicillin, 5,000 units per cc., should be used Acetic acid in 1 per cent solution is valuable for Bacillus pyocyaneus infections.

Warm foot soaks.—For open lesions, normal saline soaks for one hour once or twice a day at 35–38 C. (95–100.4 F.) have proved most satisfactory Between soaks the extremity should be kept dry and warm under a cradle. This allows softening of the crusts, thereby aiding free drainage of any infected areas.

Contrast baths.—These have long been recommended for increasing the local circulation Two large containers are used, one containing water at about 38 C. (100.4 F.), and the other, water at 10–15 C (50–59 F.). For the lower extremities the water should nearly reach the knees. The patient should place his legs (or arms) in the hot water for three minutes, then the cold for one minute, and to alternate in this manner seven or nine times, ending with the hot water. The object of this treatment is to encourage exercise of the vessels by producing alternating vasodilatation and constriction We have discontinued their use in favor of warm foot soaks and sitz baths.

Tub or modified sitz baths—The repeated production of the vasoconstrictive phase may be more injurious than helpful, and to encourage vasodilatation of the collateral vessels from the higher levels we have practically abandoned the contrast bath in favor of a modified sitz bath. The patient is instructed to sit in a tub containing 12 in of water at 38 C (100.4 F) for 30 minutes once or twice daily If the involvement is extensive, a slightly lower temperature of about 35 C. (95 F.) should be used These baths are more satisfactory and less painful than contrast baths. We recommend this form of treatment when the problem is one of obviously impaired circulation with threatened rather than actual ulceration or gangrene.

Antiseptics—The use of strong antiseptics such as iodine, phenol, silver salts and the mercurials should be mentioned only

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of a specially built incline or by pillows or the back of a chair inverted at an angle of 45–60 degrees above the horizontal. The legs are (1) elevated on this incline for 2–3 minutes, (2) lowered over the edge of the bed for 5–10 minutes, and (3) rested at bed level (horizontal) for 5–10 minutes. The cycle is repeated five to ten times, two to three times a day.

The color changes—blanching on elevation and rubor on dependency—clearly indicate the movement of blood draining from and filling the vascular tree The physician should determine the timing on the basis of the actual time required for blanching on elevation and development of rubor on dependency For example, on the basis of trials with a specific patient one might prescribe elevation 1½ minute, dependency 3 minutes and rest 3 minutes (an arbitrary figure). Study of the patient a month later might warrant revision of these figures according to the improvement or retrogression that has taken place Recent criticisms of active exercises are based on inconclusive data

(b) A W Allen's modification of this procedure is helpful if the feet are not too painful

During the second phase, when the legs are hanging over the edge of the bed, the feet are further exercised. (1) The feet are extended downward (2) The feet are then raised by flexion at the ankle joint (not by raising the legs) (3) The toes are turned inward as far as possible. (4) The toes are turned outward as far as possible (5) With the feet in normal position the toes are spread open (6) The toes are closed This is repeated during the dependent phase of each cycle

(c) Oscillating bed This type of motorized hospital bed which slowly raises the head (lowering the feet) and then raises the feet (lowering the head), provides continuous exercise of the Buerger type up to 24 hours a day After years of experience with a large number of patients I believe this bed offers distinct advantages over other forms of active and passive vascular exercise A complete discussion appears on page 145 Since response to typhoid vaccine and the other methods outlined is so satisfactory, the oscillating bed is seldom needed in treatment of thromboangiitis.

to be condemned. Although bactericidal, they all tend to injure the tissue cells, and when the most delicate tissue cells—those of the new fingers of epithelial growth—are trying to extend, such substances may retard and destroy them. The colored dyes such as gentian violet and scarlet red obscure the clinical picture, which is evaluated largely by color changes, without producing compensating results. Mild substances, such as boric acid solution, saline and occasionally alcohol, are preferablé. For Bacillus pyocyaneus infections (characterized by bright green pus) acetic acid in 1–2 per cent solution as a wet dressing is efficacious.

Antibiotics.—Penicillin, 5,000 units per cc., as a wet dressing for lesions infected with staphylococci and streptococci has given gratifying results It should also be given parenterally if there is evidence of systemic infection. We have given from 240,000 to 1,500,000 units a day, depending on the severity of the infection. The value of streptomycin for such lesions must be determined by further study.

Ointments and salves.—The only safe type of ointment is penicillin in cod liver oil ointment, 5,000 units per Gm. Its use should be discontinued when infection has subsided. In general, I have found other ointments and salves unsatisfactory. They appear to retard healing and prevent drying of the lesions, which is the opposite of the effect desired Ointments intended to alleviate pain have been especially disappointing, failing for the most part to achieve their purpose and tending to retard healing by the action of their chemical constituents on the delicate granulation and epithelial tissues

Vascular exercises.—(*a*) Buerger's exercises. Various slight modifications of the exercises described by Buerger have been used widely to exercise the vascular tree, clear away stagnant blood and stimulate the opening of collateral vessels. The following technic is recommended.

The patient rests on his back in bed Beginning at the patient's hip level, an elevation extending to the foot of the bed is achieved by means

of a specially built incline or by pillows or the back of a chair inverted at an angle of 45–60 degrees above the horizontal The legs are (1) elevated on this incline for 2–3 minutes, (2) lowered over the edge of the bed for 5–10 minutes, and (3) rested at bed level (horizontal) for 5–10 minutes The cycle is repeated five to ten times, two to three times a day.

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The foregoing procedures used judiciously have proved highly satisfactory in the treatment of patients whose record of healed ulcers and gangrenous areas would have been considered impossible 15 years ago. Others have claimed satisfactory results with various other methods which should be mentioned for the sake of completeness and possible use in case of failure of the régime already discussed. It should again be emphasized that all modern workers insist first of all on total abstinence from tobacco.

Saline and other solutions intravenously.—Since the observations of Mayesima that the viscosity of the blood is increased in thromboangiitis obliterans, various solutions have been used on the theory that reduction of viscosity would favorably affect the course. Koga introduced intravenous therapy in thromboangiitis obliterans, using physiologic sodium chloride in some cases and Ringer's solution in others. Willy Meyer was the first American to adopt this method, using the same solutions. Ginsberg and Steel used sodium citrate. Various other solutions were then tried. That most widely used today is hypertonic (3–5 per cent) sodium chloride, introduced by Silbert The dosage is usually 300–400 cc. intravenously three to seven times a week. Favorable results have been reported repeatedly by Silbert and by Samuels The mechanism of action has not been clearly demonstrated, although various explanations have been advanced, including reduced viscosity, increased pulse volume and vasodilatation.

The intravenous injection of large volumes of saline or citrate has been abandoned by numerous workers in favor of the régime already outlined. Typhoid vaccine gives more rapid response, more prompt relief of pain and satisfactory healing. Hypertonic saline, especially the 5 per cent solution, has caused venous thrombosis, chills and hepatitis.* Although not a treatment of first choice, when typhoid vaccine is contraindicated or response to vaccine is not satisfactory, it may be tried.

* Perhaps due to homologous serum jaundice transmitted by use of the same equipment for many patients—a hazardous practice

Sodium citrate, Ringer's solution and insulin for the treatment of thromboangiitis obliterans have been abandoned in most clinics. Further discussion of them is not, therefore, indicated

Alternating pressure and suction.—The use of alternating pressure and suction in the treatment of vascular disease was given impetus by the work of Landis and Herrmann and their co-workers (p 143) The first results reported in thromboangiitis obliterans were encouraging, but later experience has been disappointing The fact that its use is contraindicated in the presence of phlebitis and infection rules out many cases of thromboangiitis obliterans. In one series of 10 cases of which I have knowledge, acute phlebitis developed in seven during treatment. I discontinued its use in thromboangiitis obliterans very early because the results were not encouraging Certainly when used alone this treatment was not as satisfactory as typhoid vaccine therapy. There seems little justification for the use of elaborate and expensive equipment requiring special supervision when an inexpensive dose of vaccine will produce the same or better results

Intermittent venous occlusion.—The use of intermittent venous occlusion in the treatment of vascular disease was favorably reported on by Collens and Wilensky (see p 145) After nearly a year of conscientious study of the effects on numerous patients we abandoned the procedure because of inability to attribute definite responses to its use Other workers have also given it up after extensive trial

SURGERY

In the treatment of thromboangiitis obliterans there has been a steady trend away from early amputation toward a conservative regimen in which amputation of more than a digit is extremely rare The results of this evolution have been as striking as those following the discovery of insulin and the administration of liver for pernicious anemia, but have not received like recognition be-

cause success came from the efforts of many workers rather than from a single dramatic discovery of one man.

Surgical skill is requisite for the handling of ulcers and minor amputations and for the occasional nerve section or crushing for extreme pain In some clinics sympathetic surgery, including ganglionectomy, is still being done, but it is rarely necessary since the disease can be controlled satisfactorily by the simple procedures already outlined Sympathetic surgery should be undertaken only when (1) simpler measures have failed or act too slowly, (2) good results are assured by evidence from a procaine ganglionic block (recently this test has been shown to be unreliable in some cases), and (3) the patient has definitely stopped smoking for one month and gives positive evidence of being willing and able to continue this abstinence—otherwise the operation will fail. We have seen numerous examples of massive gangrene following ganglionectomies by highly skilled surgeons because the patient continued to smoke or recommenced smoking.

The proper use of heat, wet dressings and antiseptics and warning against unwise paring of corns and calluses have been presented. To these remarks should be added warnings against the removal of firmly fixed nails and incision of toes. These procedures have great potential danger when thromboangiitis obliterans is present *No* operation on the feet or hands should be performed until the status of the circulation has been determined I have seen two patients within 18 months in whom procaine, with epinephrine added, was injected around the base of a digit preparatory to the opening of what was considered a minor infection. The digit in both instances promptly turned black and never regained normal color Both were lost. *After* the digit was damaged beyond repair the surgeon discovered that the major vessel leading to the area was occluded and a diagnosis of thromboangiitis obliterans was made. One minute devoted to palpation *prior* to the anesthesia would have prevented the serious consequences. In these patients epinephrine should never be mixed with procaine for such a procedure,

for the life of the tissues often depends on the superficial collateral vessels which sometimes cannot react after violent constriction by epinephrine.

In general, our policy is to allow a gangrenous part to demarcate and to permit spontaneous amputation of the digit as far as possible. Slight surgical aid is sometimes necessary to hasten the termination of this process, but rarely is anesthesia needed. The foot is placed in the best position to facilitate drainage, whether the patient is forced to lie on his back or on his abdomen. For the surgical technics the reader is referred to the many textbooks and articles on the subject and to Pratt's excellent summary in his monograph, *Surgical Management of Vascular Diseases.*

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the eating of rye bread made of flour ground in the 1951 season The ergot fungus grows best in wet weather and this was one of the wettest seasons in many years in that area The last previous severe epidemic in the same general area was in Burgundy and in Lorraine in 1816, although sporadic cases have cropped up since

Fairly recent descriptions of the epidemic syndrome as it has occurred in Russia indicate that the onset is often accompanied by diarrhea, nausea or vomiting and colic. The extremities then become cold, ruboric or bluish and numb. The pulse is diminished and necrosis, either moist or dry, commences. The nails are usually lost Gangrenous blebs may develop and spread rapidly to include the whole extremity. It should be noted that other areas of skin may be involved, including the nose and ears Buerger stated that the malady might be latent until a severe disease such as pneumonia develops which may lead to massive lesions such as gangrene of the lungs, intestines or female sex organs.

The first therapeutic use of ergot also dates far back in history, being mentioned as a recognized procedure in 1774 (Borger). The relationship of ergot therapy to the development of gangrene has not long been accepted, yet gangrene does follow ergot therapy and with the increased use of ergot preparations will probably assume greater importance.

Yater and Cahill reported a case of bilateral gangrene of the feet due to ergotamine tartrate administered for pruritus of jaundice. The case is significant because the patient was under observation throughout the illness, and the diagnosis was established by histologic evidence typical of ergotism The walls of the arteries were thickened and the intima was concentrically or eccentrically infolded The lumens were either occluded by folded intima or filled with thrombi in the less constricted segments. The walls of all the vessels showed hyaline degeneration involving both media and intima. The internal and external elastic laminae were fairly well preserved but broken in a few places. Just proximal to the gangrenous area some of the small arteries showed changes highly

CHAPTER V Ergotism

ERGOTISM, especially in epidemic form, has been recognized for centuries, although the etiology was not established until the nineteenth century. It was then associated with use of rye containing the fungus ergot. Mezeray described epidemics in France in 944 and 1090 A.D. Two distinct forms of the condition have been recognized the convulsive, and the gangrenous. In medieval times the gangrenous type was most prevalent in France, while convulsive ergotism occurred with greater frequency east of the Rhine River. No differences in the ergot could be detected, and the explanation for the geographic variation in manifestations has never been clear. The gangrenous type, known for centuries as St. Anthony's disease, attacked the extremities, with extreme rubor and burning pain, followed by dry, black mummification of the limb. The convulsive type produced periodic distortions, with twisting of the limbs and even the body. Epidemics have been described in Russia, England, Algeria, Sweden, Norway, Finland, Hungary, Austria, Germany, France and elsewhere.

Although outbreaks of epidemic ergotism have been rare since the advent of modern agricultural methods the risk is still present. In August, 1951, a report came from Port-Saint Esprit near Avignon in the Rhone Valley of the most extensive outbreak in many years. Four people died and some 90 were afflicted by the severe convulsive type with acute disorientation and manic states. Some felt as if they were surrounded with flames, others that they were being pursued; several attempted suicide. This epidemic arose from

the circulation and so does not cause gangrene directly. The spasm profoundly slows the blood stream and leads to the secondary changes in the vessels described" (*thrombi that are due to stasis* from injury to the endothelium and to the loss of plasma)



FIG 50—Ergot poisoning. Nearly complete healing of superficial gangrene of tips of toes of left foot of patient who had marked diminution of pulsations in all extremities and gangrene of the toes (From Medichrome Series MM—Vascular Diseases, by I. S. Wright and W T Foley)

The possible relationship of ergotism and thromboangiitis obliterans is discussed in Chapter IV.

Kaunitz and McGrath have re-emphasized the fact that epidemic ergotism occurs predominantly in males, as does thromboangiitis obliterans, and that there is a resemblance pathologically McGrath demonstrated that whereas gangrene could be produced in the tails of rats of both sexes, females could be protected by large doses of theelin but males were incompletely protected. Possibly

suggestive of proliferation of the intima, in some instances being almost completely obliterated by cells. Within the gangrenous area the walls of the small arteries and veins showed various degrees of secondary inflammatory reaction and a few small veins contained thrombi.

Although not numerous, the reported cases of gangrene or threatened gangrene following ergot medication deserve attention. A number have been associated with the puerperium with or without sepsis Gangrene, of course, occurs in patients with severe puerperal infection who have not taken ergot, but the possible relationship deserves serious consideration when any form of the drug is prescribed. Gangrene of the extremities has been reported following the administration of ergotamine tartrate for exophthalmic goiter. These cases have been, in general, less severe and most of them have ended in recovery. The onset and development of the gangrene in these cases closely resemble the course of epidemic ergotism described earlier. One patient had diminished pulsations in all extremities and gangrene of the toes of the left foot after imbibing 24 cc. of fluidextract of ergot within 36 hours before hospitalization A left lumbar sympathectomy was performed promptly, and with rest and administration of vasodilating drugs recovery was slow but good, with all toes healed within one month. (Fig 50).

Other symptoms that may develop following the use of ergot are headache, dizziness, nausea, vomiting, diarrhea, weakness, formication and itching, coldness of the skin, cyanosis, syncope, collapse, confusion, drowsiness, depression, thirst, anginal pains, increase or decrease in heart rate and blood pressure, amblyopia, cataract, twitching, muscular cramps, convulsions and hemiplegia with sudden death.

Gangrene has repeatedly been produced in lower animals by means of ergot since von Recklinghausen studied the histology of the cock's comb On the basis of more recent work Lewis concluded that the "vascular spasm in ergot poisoning does not arrest

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in both ergot poisoning and thromboangiitis obliterans the female is protected by a sex hormone, probably the estrogenic substance of the ovary. It may be that the male, during the years of sexual potency, has a mechanism possibly related to hormone metabolism which renders him susceptible, inasmuch as thromboangiitis obliterans does not have its onset after the climacteric.

Prevention and Treatment

Ergot-containing substances should not be administered to any patient known to have a vascular disease. The presence of an acute infection also is a contraindication. Even in patients with febrile puerperium it should be used only with hesitancy Small test doses for susceptibility may be tried, but they probably have slight preventive value. Avoidance of long-continued use of the drug and careful study of the patient during its use are vital.

The slightest toxic manifestations, local or general, are an indication for immediate discontinuance of the drug The following measures, although empiric, should be instituted to produce vasodilatation application of blankets and controlled heat to 90–96 F. by means of a thermostatic cradle or hot water bags; whisky, ½ oz. every four hours, papaverine hydrochloride, ½ gr. intravenously every four hours, 25 mg Priscoline or 0 06 Gm papaverine intra-arterially in the affected extremity, and other vasodilating methods to be tried until danger of gangrene is past. Lumbar sympathetic block has also been effective.

Once susceptibility to ergot is demonstrated, the individual should probably never take it again

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CHAPTER VI Raynaud's Syndrome and Related Conditions

THE ORIGINAL DESCRIPTION of the syndrome producing symmetrical gangrene published by Raynaud in 1862 included not only Raynaud's syndrome as we know it today but, in all probability, some thromboangiitis obliterans and perhaps other diseases.

Raynaud's syndrome as it is known today has the following characteristics. (1) There are intermittent changes in the color of local areas produced by cold, emotional disturbances or the use of machines with high vibration rates such as pneumatic hammers. (2) Color changes are characterized by a yellowish pallor or striking cyanosis during the attack, followed by compensatory erythema when the attack subsides on entrance into a warm environment, release from emotional tension or discontinuation of the use of a vibrating machine (see Figs 56 and 57). (3) Although in the early stages involvement may be unilateral or even confined to a single digit, as the disease progresses it usually becomes symmetrical or bilateral. The traumatic vasospastic cases may continue to be unilateral if, for example, only one hand is used to hold the vibrating machine. It may otherwise involve both hands, both feet, both ears, both cheeks or both sides of the nose, or any combination of these areas. (4) In the early stages there are no occlusive lesions of the arteries. Later, after innumerable attacks of spasm, organic occlusive changes may take place in the arteries. (5) Gangrene or trophic changes may occur late in

the disease. Usually these are limited in large degree to the skin. Today one rarely encounters massive gangrene of the fingers or toes as a result of Raynaud's syndrome.

Etiology

The fundamental etiologic factor in Raynaud's syndrome is not known. No specific agent has been found to be responsible It is not even established that it is on a viral, bacterial, allergic, hormonal or some entirely different basis. Certain stimuli, however, are known to be capable of initiating individual attacks.

Cold.—Cold is the commonest and principal factor. An individual with Raynaud's syndrome, when exposed to cold of sufficient degree, develops vascular spasm in the affected areas that is not relieved until the environmental temperature is increased The reaction to cold differs considerably from patient to patient. In some the temperature must be quite low, i e, 4.5–7.3 C (40–45 F.). In others who are more sensitive to cold, an attack is precipitated at 18.3–21 1 C. (65–70 F.); reactions are not infrequent during swimming in water at such temperatures.

It is frequently difficult to induce spasm by having the patient put his hand in a basin of ice water, a test commonly used in study of these patients. In ice water the vessels may become paralyzed, the blood does not give up its oxygen and the hand may remain bright red instead of going through the characteristic changes of Raynaud's syndrome When the body of the same patient is chilled, as when entirely exposed to cold air, typical Raynaud's phenomena of the hands may be seen. On the other hand, as Lewis has pointed out, in some patients a cold stimulus applied to the base of a finger may cause a typical attack of vasospasm limited to that finger. As a result of this reaction to cold the syndrome is usually much more pronounced and troublesome in winter than in summer and in temperate than in tropical climates However, highly sensitized patients with advanced cases

CHAPTER VI Raynaud's Syndrome and Related Conditions

THE ORIGINAL DESCRIPTION of the syndrome producing symmetrical gangrene published by Raynaud in 1862 included not only Raynaud's syndrome as we know it today but, in all probability, some thromboangiitis obliterans and perhaps other diseases.

Raynaud's syndrome as it is known today has the following characteristics. (1) There are intermittent changes in the color of local areas produced by cold, emotional disturbances or the use of machines with high vibration rates such as pneumatic hammers (2) Color changes are characterized by a yellowish pallor or striking cyanosis during the attack, followed by compensatory erythema when the attack subsides on entrance into a warm environment, release from emotional tension or discontinuation of the use of a vibrating machine (see Figs. 56 and 57). (3) Although in the early stages involvement may be unilateral or even confined to a single digit, as the disease progresses it usually becomes symmetrical or bilateral. The traumatic vasospastic cases may continue to be unilateral if, for example, only one hand is used to hold the vibrating machine. It may otherwise involve both hands, both feet, both ears, both cheeks or both sides of the nose, or any combination of these areas. (4) In the early stages there are no occlusive lesions of the arteries. Later, after innumerable attacks of spasm, organic occlusive changes may take place in the arteries. (5) Gangrene or trophic changes may occur late in

Rome in 1911 and first reported in this country by Cottingham in 1917. Cottingham made his investigation, at the request of the Journeymen Stone Cutters Association, on men using pneumatic chisels in Indiana limestone quarries Dr. Alice Hamilton thereupon went to Indiana to study the problem and reported on it in 1918.

Since then it has become increasingly realized that "pneumatic hammer disease" is too restricted a term and that the condition should be known as "traumatic vasospastic disease" producing Raynaud's syndrome, for many other etiologic factors have been found. These include work with tools used in shipbuilding, locomotive and other workshops, airplane construction, shoemaking—all tools of high vibration In addition, I have encountered the syndrome in several typists, two concert pianists, a telephone operator and a handball expert. One pianist was forced to give up a successful career. The telephone operator had the syndrome in one hand which she used for "plugging in" on the switchboard to the point where superficial gangrene developed. Following our advice she changed hands for her work, using the unaffected hand. Within a few months, however, this hand became similarly involved, in one sense proving to be an interesting experiment. Most patients continue to have the vasospastic phenomena as long as they remain at their occupations Unless a change from the occupation is made during the early stages of the syndrome, the condition may be irreversible and in fact may be progressive.

Occlusive arterial disease.—Physicians generally do not realize that the early stages of occlusive arterial disease may be associated with Raynaud's syndrome. In such cases the syndrome is probably due to the fact that, with their lumens narrowed and walls damaged, the vessels are very susceptible to irritation such as cold and to spasm, becoming capable of producing the syndrome. The condition is relatively common during the early stages of thromboangiitis obliterans It is uncommon with arteriosclerosis, although I have seen several patients with Raynaud's syndrome prior to the

continue to have spasms in warm climates when there is a relative drop in the temperature.

Emotion.—The second factor of great importance in the production of attacks is emotion. Anger, fear and excitement may each be capable of causing attacks in certain individuals. In some patients the emotional disturbances accentuate the effects of cold, in others, attacks may be produced by emotional stimuli alone and even in a warm room. An example of this response was seen in a young woman lawyer assigned as a defense counsel in the trials of Japanese war criminals. She became very disturbed and developed atypical Raynaud's syndrome with gangrene of one finger. This healed on her return to the States, but manifestations of the syndrome recur on exposure to cold or to emotional disturbance.

Cryoglobulinemia.—This uncommon condition is encountered most often with multiple myeloma, kala-azar, arthritis, hepatic disease, lupus and, rarely, with other diseases. Characterized by the occurrence of cold-precipitable agglutinins in the serum or plasma, it may be responsible for what appears clinically to be the Raynaud syndrome. Actually the mechanism is based on the agglomeration of the blood cells as they become enmeshed in a precipitate of cryoglobulin when the temperature of the blood in the digit falls below 37 C. The digit then becomes cyanotic or pale. When the blood is warmed above 37 C, it resumes its fluid state and moves along, allowing bright red fresh blood to replace it and produce an erythema. Probably spasm typical of the true Raynaud's syndrome plays little or no part in this picture. If, however, the precipitation persists too long, ischemia of the tissues may result in gangrene. We observed this in a patient seen through the courtesy of Dr. David Barr. This patient had gangrene of fingers and toes as well as of ears and nose.

Traumatic vasospastic disease.—Some years ago it was recognized that individuals who handle vibrating tools may develop circulatory disturbances in the hands. This was formerly known as "pneumatic hammer disease." It was first described by Loriga of

of Raynaud's syndrome, Allen and Brown found that 133 were females. Of the 17 males only seven had all the criteria and the other 10 were given the diagnosis of probable Raynaud's syndrome. In 1945 Hines and Christensen again analyzed the incidence at Mayo Clinic. Of 840 patients with the diagnosis of Raynaud's syndrome, 649 (77 per cent) were females and 191 (23 per cent) males, despite the fact that the sex incidence of admissions to the Clinic during the period was about equal

In our experience the ratio in males and females is approximately 30:70. Our figures do not include cases of thromboangiitis obliterans with Raynaud's syndrome, being limited to those considered to be cases of pure Raynaud's disease, which is one of the conditions producing Raynaud's syndrome.

Arsenical poisoning of a mild chronic nature and *disturbed calcium metabolism* have been mentioned as causative factors, but the evidence is inconclusive. It is true that calcium disturbances in the blood, bones and soft tissues frequently accompany the sclerodermatous syndrome

Pathology and Pathologic Physiology

Major pathologic changes are rare in Raynaud's syndrome. The early manifestations of the disease seem to be on a vasomotor basis without demonstrable pathology in the nervous system. Pathologic changes have been reported in the sympathetic ganglions and in the spinal cord, but they have not been satisfactorily confirmed Late in the disease, local changes may occur in the small arteries, with a tendency toward thickening of the walls and occlusion. They appear to be secondary to innumerable episodes of vasoconstriction. Similar lesions have been noted in the ears of rabbits after production of vasospasm by the injection of nicotine. Occlusion is rare in vessels larger than those of the digits In late cases, the capillaries of the nail fold reveal a characteristic picture. Dilatation is striking, primarily in the venous limb of the loop

development of arterial occlusion with gangrene. Following this, Raynaud's syndrome gradually faded to minor significance. In a statistical analysis Allen and Brown found among 200 cases of thromboangiitis obliterans that Raynaud's syndrome was the first symptom in 12 per cent and that it occurred some time during the course in 30 per cent of all cases. Hines and Barker found in 280 cases of arteriosclerosis obliterans that Raynaud's syndrome had been present in 10 per cent.

Hyperabduction and other shoulder girdle syndromes.—It has been noted for some years that the Raynaud syndrome is occasionally encountered in association with a cervical rib or scalenus anticus syndrome. No special attention has been focused on this point. When these patients were operated on, a few had lessening of the Raynaud phenomena

In 54 patients with the hyperabduction syndrome reported on by Beyer and myself, we were impressed to find that 20 had a true Raynaud syndrome. This incidence is so greatly in excess of that encountered in the general population that it cannot be considered due to chance Furthermore we have been able to abolish the signs of Raynaud syndrome in a small number of these patients by the simple measure of teaching them to avoid the position of hyperabduction in their sleep or their work. This is dealt with in greater detail in Chapter X in the discussion of the hyperabduction syndrome.

Huebner, Lord and I are studying the surgical exploration of the shoulder girdles in some intractable cases and have found that in some the pinching and tension of the brachial plexus and subclavian axillary arteries and veins are of a great and highly irritating order. This work suggests that sympathetic surgery may not be the only approach.

Raynaud's syndrome is also seen more often than usual in other conditions, including *rheumatoid arthritis*, progressive muscular dystrophy and other diseases of the muscles.

Sex.—Of 150 patients in a Mayo Clinic series with the diagnosis

of vibrating machines should be considered to have early or moderate Raynaud's syndrome.

The nail fold capillaries during the cycle of an attack present a good picture of the local pathologic physiology. In the first phase, that of waxy pallor, few capillaries can be seen. Filling of the loops is incomplete and they have a segmented broken appearance due to the fact that the walls are invisible and the column of blood cells is interrupted and static. No blood is entering the capillaries from the arterioles, which are in spasm. The surface temperature of the involved area is low. After a short time, it approximates room temperature In some instances there is intermittent leakage from the arterioles and by retrograde flow from the venules, so that the capillaries become more easily visible, in fact even distended The blood is relatively static also, and as deoxygenation takes place the part assumes a cyanotic color. There may be patches of cyanosis and rubor during this phase. With cessation of the attack the arterioles open, pouring blood rapidly into the capillaries and other minute vessels, which then become markedly dilated with bright red oxygenated blood. Some areas may remain cyanotic for a while because the supplying arterioles do not open simultaneously at all points The surface temperature of the erythematous areas rises rapidly to above the average normal (30.5–33 9 C.; 86–93 F.) during this phase.

SCLERODERMA AND CALCINOSIS

Scleroderma of the affected parts is a common complication of Raynaud's syndrome. In the involved areas the skin becomes tightly stretched and the malpighian layers are atrophied. The deeper layers become fibrosed. Histologic examination shows hypertrophy of the collagen and stratum granulosum. The fibrosis extends into the subcutaneous layers and muscles and may even bind the skin to bones lying relatively near the surface. Arteries such as those in the digits are surrounded by fibrous tissue. Their

(Fig. 51) and gradually extending toward the arterial limb The dilatation may be due to the repeated erythematous phases, following the spastic phenomena, during which time the loops are filled with blood to the point of overstretching.

Whether the gangrene of Raynaud's syndrome is due to a local circulatory fault or to a purely vasomotor phenomenon frequently repeated and with sufficient severity to produce anoxemia to the tissues to the point of death has long been a subject of debate. It seems likely that both factors play a part. The original attacks are



Fig 51 —Raynaud's syndrome Remarkable dilatation of capillaries during a period of hyperemia, most marked in venous limb

probably due to vasomotor phenomena alone, and repetition of these phenomena gradually damages the local arteries, followed by ischemia and death of the cells which the arteries normally supply. Gangrene only occurs in severe cases. I have observed numerous individuals who have had Raynaud's syndrome of mild or moderate degree for many years without gangrene and without progression.

Formerly it was thought that the presence of actual gangrene was essential to justify the diagnosis of Raynaud's syndrome. This view is no longer held. Raynaud's syndrome should be recognized in its early phases and so classified. In other words, patients who do not have gangrene or trophic changes but who manifest the characteristic color changes in response to cold, emotion or the use

posits of calcium, usually mixed with phosphates, cholesterol and various other components, are scattered in numerous areas, but most frequently in the skin, subcutaneous tissues and muscles

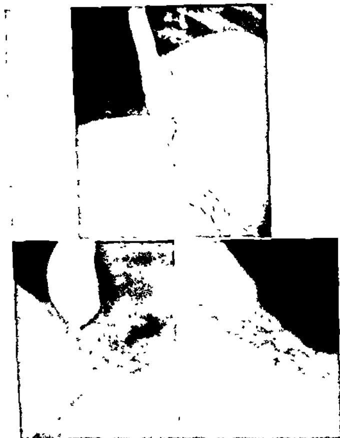


FIG. 53.—Examples of sclerodermatous involvement of esophagus, with stricture of cardiac end.

The commonest sites are exposed areas over joints such as the outer surfaces of the knees, elbows and finger joints The nodules may penetrate the skin, protruding as horny masses. They are often

channels are narrowed by intimal thickening and the external pressure from the fibrosis. Pigmentation of the skin occurs at this time. Marked bony change of several varieties may take place. Arthritic changes may be either atrophic or hypertrophic. These

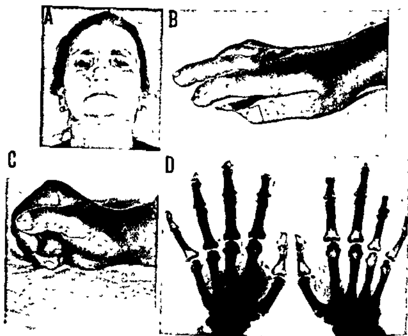


FIG. 52 —Scleroderma *A*, after five years duration features are masklike and [illegible] aximal movement [illegible] fingers after 170 [illegible] with loss of ter

changes combine with the fibrotic changes of the soft tissues and often result in ankylosis of the joint, usually in a somewhat flexed position Atrophy of the terminal digital phalanges, beginning at the tip and gradually destroying the entire phalanx, is common.

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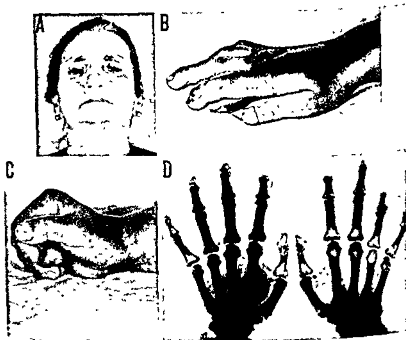


FIG. 52.—Scleroderma *A*, after five years' duration, features are masklike and jaw motion is limited *B*, marked involvement of hands, with maximal movement 10 degrees; trophic changes in finger-tips *C*, ability to flex fingers after 170 treatments with Mecholyl ion transfer *D*, typical bone changes, with loss of terminal tufts and decalcification with some hypertrophic changes

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ever, one may be overzealous in this regard, as in a case I followed for about 10 years.

A man had definite clinical, steadily progressive scleroderma with Raynaud's syndrome of more than 13 years' *duration involving the* hands, face and skin of most of the trunk. For four years he had had

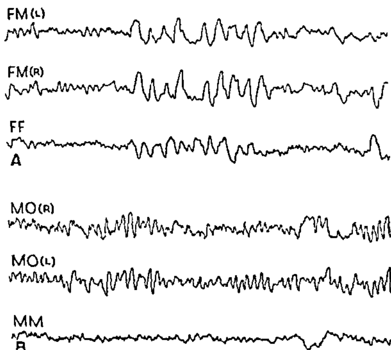


Fig 54—Electroencephalograms showing abnormal cerebral activity with scleroderma *A*, abnormality in frontal motor leads, note high amplitude and 4 cycle per second serial waves *B*, abnormality in motor occipital leads, with slightly greater activity on left

difficulty with regurgitation, and two sets of x-rays were interpreted by competent radiologists as showing changes at the cardiac end of the esophagus compatible with scleroderma Roentgenographic studies of the lungs also suggested scleroderma, although a history of a month or so in mines with a high silica content 30 years before was considered.

so painful as to necessitate surgical removal, even though healing may be poor and recurrence of the local calcinosis is likely. The process cannot easily be distinguished from the calcinosis seen occasionally as a result of massive doses of vitamin D. The associated scleroderma, the penetration of the skin (which is rare in the pure vitamin D cases) and the lack of history of ingestion of vitamin D are distinguishing features. However, through the courtesy of Dr Richard Freyberg, I saw a patient with scleroderma who had received massive doses of vitamin D for so-called "scleroderma arthritis" with a rapid and serious onset of calcinosis—thus confusing the etiologic picture thoroughly.

Scleroderma may involve any area of the surface of the body and also the internal organs, including especially the larynx, esophagus (Fig 53), lungs, kidneys, bladder and gastrointestinal tract below the stomach We have seen women in whom scleroderma tightened the vaginal opening to the point where intercourse was impossible and men in whom involvement of the penis caused constant semi-erection. A few cases of scleroderma heart disease have been described, and abnormal electroencephalographic readings recorded (Fig. 54). Thus scleroderma is a diffuse systemic disease involving the collagenous tissues wherever they may be found Frequently it is associated with Raynaud's syndrome of the hands.

In the heart, the primary lesion of scleroderma seems to be an overgrowth of collagenous fibers in focal areas throughout the myocardium. It may also involve the endocardium and pericardium. There does not appear to be any relation between the fibrotic areas and vascular lesions. Involvement of the coronary arteries and their branches is not characteristic. The lungs, when involved, show diffuse interstitial fibrosis (Fig 55). Many of the alveolar spaces are obliterated. There is frequently marked thickening of the pleura by collagenous tissue. Collagenous fibrosis may be found throughout the kidneys. When scleroderma of the skin begins to spread one must constantly bear in mind the possibility of extensive involvement of the deeper organs. Occasionally, how-

disease on the basis of the tightening and feeling of thickness of the skin, yet the pathologist was unable to confirm the diagnosis. The end of the esophagus, diagnosed twice by roentgenologists as having changes suggestive of scleroderma, was considered by the pathologist to be entirely normal. Fibrosis of the lungs was definitely present but was attributed to long-standing silicosis. The heart block was caused not by sclerodermatous changes but by a bar of calcium extending from the mitral valve in such a way as to sever the bundle of His. Thus our beautiful picture of multiple pathology from a single disease was destroyed The case is cited to emphasize the problems involved in diagnosis

In the presence of scleroderma, skin capillaries are seen with difficulty. They are scattered and constricted, and occasionally a dilated one is found. Stretching of a finger obliterates them and the skin blanches Relaxation of the finger brings a few more capillaries into action, but observation is difficult even with the best capillary microscopy.

Signs, Symptoms and Course

Raynaud's syndrome should be classified in two different ways. First, there is the acute cycle which is repeated innumerable times in the course. This has already been described Second, on the long term basis there are four stages of development. This is important because study of a large number of patients discloses that the signs and symptoms of any of the four stages may progress, remain in statu quo or tend toward improvement, regardless of any therapy thus far devised The exception to this statement is discussed under the heading of surgery for Raynaud's syndrome.

1. *Early Raynaud's syndrome*.—This is sometimes called the pre-Raynaud syndrome. In this stage are classed the mildest cases, many of which do not progress, merely showing a spastic response to cold throughout the patient's life without demonstrable pathology ever developing This is highly important in prognosis Many patients have been told by physicians that they have Raynaud's disease and that they must anticipate the development of gangrene

Three months before death a 2:1 heart block suddenly developed The rate dropped to 34 beats per minute, at which time he had an attack of syncope and fell to the floor of his bathroom. After adjustment to the low rate, a fairly satisfactory compensation developed and he went back to business It was thought that there were probably sclerodermatous changes in the heart Two days before death he had a second sudden



FIG 55—Pulmonary changes with generalized scleroderma

attack of syncope and the heart rate was 30. It is possible that normal rhythm had returned and acute heart block once more developed This [illegible] later he sat

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many of the classic signs of sclerodermatous involvement of the deeper [illegible] of the skin,

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of the fingers Nothing could be less sound than such a statement, since the development of gangrene in this disease is now extremely rare and for every patient in whom gangrene develops there are many patients in whom the disease never progresses beyond the stage of episodic blanching. Some patients do show progression, but it is impossible to predict without consecutive observation or a detailed and long history which cases are benign and which are seriously progressive. Some progress very slowly until middle life, after which the syndrome remains stationary or actually improves A typical attack involving the hands, although other parts may react similarly, may be described as follows (Figs. 56 and 57).

Following exposure to stimulation such as cold or an emotional upset, the arterioles develop spasm, the blood becomes static and the hands begin to blanch, turning grayish owing to deoxygenation. As additional vessels go into spasm, forcing the blood out, the color becomes waxy If the vessels remain patent and filled with static blood, spasm being confined to the arterioles, the fingers become increasingly cyanotic. Cyanosis may also be produced by intermittent leakage by the arterioles If the finger is cut during this period, there will be no bleeding from the waxy flesh and only slight oozing from the cyanotic areas, both being manifestations of lack of blood flow. With these changes numbness gradually increases. In extreme cold the numbness may progress to an aching type of pain, but experiencing of severe pain is rare at this stage The phase usually remains as long as there is no change in the stimulation, e g., as long as exposure to the requisite low temperature continues. The involved areas are especially susceptible to frostbite at this time.

With removal of the stimulation, e.g , cold, emotion or vibrating machine, the second phase, that of rubor, begins The affected area turns intensely red, beginning at the proximal portion (Fig. 57) The rubor spreads wavelike distally to envelop the cyanotic area completely. Some sections may briefly remain patchy, with alternating rubor and cyanosis, until all of the spastic vessels open. With this transformation sensations of pins and needles, tingling and even burning may be complained of. The finger temperature may become abnormally high. The vessels are overdilated. This phase lasts a variable length of time, usually about

20 minutes, after which the fingers gradually regain normal appearance, temperature and feeling.

These cycles may occur repeatedly on stimulation, many times a day or at much longer intervals In general it appears that the more severe and more frequent the attacks, the more apt is the condition to progress, although numerous exceptions to this rule suggest that frequency and severity are not the primary factors in progression. The attacks characteristically appear first in young adulthood, although first attacks have been noted as early as age 5 and as late as age 65. In most patients the onset occurs in the third or fourth decade. It must be noted that pallor occurs in some patients as the sole phase, without the sequence of rubor. These are usually mild cases.

2 *Trophic changes; ulcers.*—Among the first signs of progress of the condition are trophic changes at the tips of the fingers, nose, toes or ears These are characterized by small dents and scales of brownish dry skin, occasionally, but not always, preceded by tiny ulcers The ulcers may be exceedingly painful in proportion to their size, but the trophic areas are not in themselves painful. With further progression, the ulcers may involve the entire tip of the part and are apt to be excruciatingly painful They are often moist and somewhat punched out, but some are relatively superficial As an end-result of the trophic changes and ulcerations, the tips of the digits may be deformed and shortened.

3. *Scleroderma (sclerodactylia, acrosclerosis).*—It should be fully understood that there are cases of scleroderma which do not appear to be related to Raynaud's syndrome in any way One might question the inclusion of scleroderma as related to Raynaud's syndrome, but it seems justified because of the high incidence of scleroderma with this syndrome. This adds greatly to the seriousness of the problem and complicates the therapeutic approach.

With the development of scleroderma the skin becomes increasingly hard, tense, shiny and pigmented. With the fibrosis discussed under pathology, the skin becomes fixed to the bones

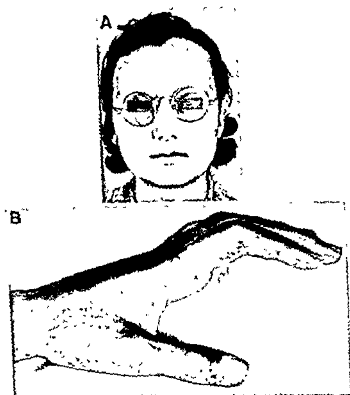


FIG 58 —Severe scleroderma in girl aged 15 *A*, beginning tightening of skin of face *B*, hand changes after 15 months Marked Raynaud's syndrome was present The patient died after four years of uremia secondary to sclerodermatous renal changes Parathyroidectomy, cervical ganglionectomy and extended courses of mecholyl ion transfer had had no effect on the course

and joints to produce fibrotic ankylosis, although the joints may not actually be involved at first. Later there is x-ray evidence of hypertrophic changes. The skin loses its natural color and there is increasing difficulty in visualizing the capillaries, which often resemble shadows without definite structure. Typical attacks of Raynaud's syndrome are then more easily produced Frequently the stage of rubor is absent because of pressure and tension of the skin and subcutaneous tissue and because pigmentation may produce a mahogany color of the skin. The symptoms of scleroderma, which may involve any portion of the extremities, trunk, face or the internal organs, depend on the area involved.

The condition known as *calcinosis* (described on p 230) may further complicate the clinical picture. Calcium may be deposited under any portion of the body surface, not infrequently at the outer surfaces of the elbows, knees, ankles and digital joints As the calcified material works its way to the surface it produces considerable discomfort and at times requires surgical extirpation to relieve the pain. Recurrence is common.

The fingers gradually become fixed in the slightly flexed position. In advanced cases of scleroderma, the hands may become useless. Characteristically, when the face is involved the expression is changed because of tightness of the skin of the forehead and cheeks and around the mouth, obliterating the wrinkles and making facial movements difficult. The mouth may be so constricted as to make the ingestion of anything but liquids almost impossible. Dental work may become out of the question. The neck may become stiffened. Numerous spider angiomas may appear, especially on the face.

4. *Gangrene.*—The fourth phase is that of frank massive gangrene involving large portions of the fingers, toes or other areas Most discussions of this complication are based on descriptions in the older literature, careful analysis of which forces the conclusion that at least some of the cases really were thromboangiitis obliterans, ergot poisoning or frostbite. As the diagnostic aspects of

Raynaud's syndrome have been clarified, the reports of massive gangrene have almost ceased However, if spasm of the arterial tree occurs with sufficient severity and frequency, organic occlusion may result from clotting or changes in the vessel wall.

TRAUMATIC VASOSPASTIC DISEASE

Although the syndrome of traumatic vasospastic disease is included under Raynaud's syndrome, certain variations in symptomatology and course require special comment. The clinical pattern of vasospastic disease of the hands is typical regardless of the kind of vibrating machine or injury responsible for the onset. After a period ranging from a few months to several years of exposure, attacks of blanching and numbness of the fingers begin Pallor is as pronounced as, if not more striking than, that seen in the typical Raynaud syndrome. Ordinarily it is not symmetrical, particularly in the early stages, even though both hands eventually are involved.

In the group produced by pneumatic hammers, in right-handed persons the second, third and fourth fingers of the left hand and the tips of the fingers of the right hand are usually involved. The incidence is more frequent in the left than in the right hand because most vibrating tools are held in the left hand, with the cutting edge against the object. The handles of some hammers may be held in the right hand.

At first the attacks occur only while the patient is working and are more pronounced in cool weather. Once the disease is established, attacks can be produced by washing the hands in cold water or on chilling of the body. Although few of these patients react to emotional disturbances, I have seen one in whom emotional upsets produced attacks Careful examination reveals a moderate decrease in the sensations of touch, pain and temperature over the affected fingers. During the attacks there is frequently a discomfort of the hands described as a "toothache-like" pain, which persists for a short time after the attack is past. Even after long periods and

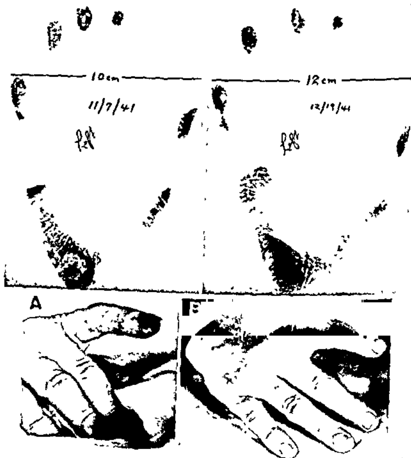


FIG 59 *(above)* —Use of hand prints for recording degree of adduction or abduction of the fingers.

FIG 60 (below).—*A*, gangrene of finger tips following Raynaud's syndrome with sclerodermatous changes *B*, healed

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many attacks the tissue does not show evidence of wasting or gangrene Scleroderma does not accompany the traumatic vasospastic syndrome. One case of scleroderma has been reported in a pneumatic hammer worker, but this was probably a coincidence.

The disease is usually limited to the hands, although some patients have complained of numbness involving one half of the body Unilateral peripheral vascular disease occurred in the left foot of a worker using this foot to operate a pneumatic drill press Examination of the blood vessels after amputation, however, revealed a typical microscopic picture of thromboangiitis obliterans In 67 cases of "white fingers" due to the air hammer, the length of use of the machine averaged 5 7 years (1½–16 years). Average duration of use among workers who had not been affected was 9 2 years, according to Hamilton. Rieder studied 250 workers who had used an air hammer up to 40 years, and of these only 75 were entirely without symptoms. White fingers were present in 86 Hamilton also reported that among 38 limestone cutters only four had never had white fingers Of 50 granite workers only seven had escaped the disorder

With change of occupation one may anticipate that the symptoms will improve slightly, they do not always disappear. Rest from the regular occupation results in improvement only if the condition is early and mild. The prognosis for complete recovery is doubtful and usually poor, although a few spontaneous recoveries have been reported Some patients who have not used an air hammer for many years still have vasospastic phenomena of the affected fingers on exposure to cold.

Gurdjian and Walker described the condition in six women war workers using pneumatic riveters in airplane construction work. The clinical picture was similar to that just described Serial sections of biopsies from the finger-tips of five of the patients were studied and compared with autopsy material obtained from the same sites, used for control. Sections were studied especially

carefully for changes in the capillaries, arterioles and veins. The capillaries appeared normal except in two sections in which a red staining substance was noted within the capillaries Similar changes were, however, noted in some of the control autopsy material and were not, therefore, considered abnormal. Larger vessels had a normal adventitial layer, the muscular coat appeared normal and the endothelial lining showed no pathologic changes in any sections studied. There was no evidence of endothelial proliferation, occlusive phenomena or inflammatory reaction in any of the sections. The pneumatic hammer used by the patients weighed 3 lb. and had a vibration rate between 3,000 and 4,000 times per minute. In the six cases, the shortest interval of use of the hammer before the condition appeared was 2½ months and the longest 11 months.

It was of interest that all employes operating this particular machine sooner or later developed vasospastic disease of the left hand Although the patients had stopped using the hammer more than a year before the report was prepared, attacks of vasospasm continued. There were no instances of bilateral involvement, as in Raynaud's disease. Nor was there scleroderma or any evidence of increased failure of proper circulation to the finger-tips, as is seen in the later stages of Raynaud's and in thromboangiitis obliterans. The condition appears to be a vasospastic disease of the fingers without organic changes in the tissues. Apparently exposure to cold is a major factor in the disorder, although other factors which must be considered are ischemia from holding the pneumatic hammer too tightly and injury to the myoneural junctions of the arterioles of the fingers.

The shortness of the period before the development of the condition in Gurdjian and Walker's cases may be due to the fact that primary vasospastic disease of the extremities is more common in women than in men.

De Takáts mentioned a case in a patient who used a small rotary air-driven tool with a vibration rate of 12,000 times per minute.

many attacks the tissue does not show evidence of wasting or gangrene. Scleroderma does not accompany the traumatic vasospastic syndrome. One case of scleroderma has been reported in a pneumatic hammer worker, but this was probably a coincidence.

The disease is usually limited to the hands, although some patients have complained of numbness involving one half of the body. Unilateral peripheral vascular disease occurred in the left foot of a worker using this foot to operate a pneumatic drill press Examination of the blood vessels after amputation, however, revealed a typical microscopic picture of thromboangiitis obliterans In 67 cases of "white fingers" due to the air hammer, the length of use of the machine averaged 5.7 years (1½–16 years). Average duration of use among workers who had not been affected was 9.2 years, according to Hamilton. Rieder studied 250 workers who had used an air hammer up to 40 years, and of these only 75 were entirely without symptoms. White fingers were present in 86. Hamilton also reported that among 38 limestone cutters only four had never had white fingers. Of 50 granite workers only seven had escaped the disorder.

With change of occupation one may anticipate that the symptoms will improve slightly, they do not always disappear. Rest from the regular occupation results in improvement only if the condition is early and mild. The prognosis for complete recovery is doubtful and usually poor, although a few spontaneous recoveries have been reported. Some patients who have not used an air hammer for many years still have vasospastic phenomena of the affected fingers on exposure to cold

Gurdjian and Walker described the condition in six women war workers using pneumatic riveters in airplane construction work. The clinical picture was similar to that just described. Serial sections of biopsies from the finger-tips of five of the patients were studied and compared with autopsy material obtained from the same sites, used for control. Sections were studied especially

In early cases the response to adequate protection is often highly satisfactory.

The best method of protecting patients from the cold is to have them remain in a warm, dry climate at least during the winter. This is impossible for many patients, however, and such a change will not control the condition if other causative factors such as emotional crises continue while in the warm climate. Winter sports and outdoor winter work should be avoided. I have seen some patients who do not have an attack while engaged in winter sports or work, but usually such exposure aggravates the condition by increasing the frequency of attacks, and the risk of frostbite in these patients when their extremities are blanched is seriously increased. If the patient must stay out of doors in the cold, warm clothing is essential. Shoes should be large enough for one or, better, two pairs of wool socks without crowding Small chemical heaters are valuable for use in pockets or muffs to keep the hands warm. Electric heaters attached to the steering wheel and automobile heaters are important for individuals who drive cars.

Local management.—It is important to avoid overheating of an area of skin in a spastic phase because severe burns may occur before the circulation is adequate to carry off the excess heat and to handle the suddenly increased metabolic demands. Any warming should be gradual and not excessive.

All strong antiseptics such as iodine, mercurials and silver salts should be avoided, for they may do more harm to the epithelization of an ulcer than to the bacteria present. Serious infection is rarely important in these cases, and mild antiseptics such as boric acid, normal saline and Azochloramid in triacetin 1:500 solution or wet dressings of penicillin 250 units per cc. should be used if needed. In general, the ulcers of Raynaud's syndrome heal best when dry. Warm soaks of normal saline at 36 7–37 8 C. (98–100 F.) should be applied for one hour each day when infection is present Wet dressings should only be used if they can

Treatment of this condition rests primarily in preventive measures, namely, the development of tools which do not require exposure to high vibration rates or in which the vibration is completely absorbed.

TREATMENT OF RAYNAUD'S SYNDROME AND SCLERODERMA

MEDICAL AND GENERAL MANAGEMENT

Reassurance.—Among the most important steps to be taken in the treatment of Raynaud's syndrome is to reassure the patient that massive gangrene of the fingers requiring major amputation is not likely to occur. Many patients are in a severe state of panic because of the implication of hopelessness, at least as far as the use of the extremities is concerned. Patients with Raynaud's syndrome often have a fairly unstable vasomotor status so that suggestion may be a powerful adjunct to other therapy. This was clearly demonstrated by Lipkin *et al.*, who studied the effects of suggestion on nine patients with a vasospastic disturbance. Six showed excellent subjective and some objective response, including relief from vasospasm for several years, subjective improvement for a year without further treatment and prolonged vasodilatation of the hands during therapy. Careful investigation into the factors responsible for the emotional instability so common in these patients and the taking of suitable rectifying measures constitute fundamental steps in any therapeutic program, in some patients constituting the most important aspects of the treatment.

Position.—When associated with the hyperabduction syndrome, relief can frequently be obtained merely by avoidance of that position. (See in Chapter X, discussion of the hyperabduction syndrome.)

Protection.—Protection from the factor producing the syndrome must be provided in all cases. This includes such variables as warm clothing, especially warm gloves, ear muffs and wool socks, the avoidance of extreme emotional crises and the cessation of a vocation or avocation that produces vasospastic phenomena.

turned off If the patient complains of a burning sensation, the treatment is discontinued immediately and the electrodes are readjusted.

Treatments are given at varying intervals from daily to biweekly, depending on the severity of the condition. Frequent treatments give the best results. Rarely is improvement seen from fewer than 20–30 treatments The drug is absorbed by the skin and increases local circulation Capillaries frequently become more easily visible. The skin gradually becomes softer and more pliable in the successful cases. Long-standing ulcers that failed to heal sometimes do heal. The response seems to be largely a local phenomenon, but sclerodermatous areas in other parts of the body may improve. This procedure is not a completely satisfactory form of treatment for scleroderma

Vasodilating drugs.—Nitrites, papaverine and similar vasodilating drugs seem to have no effect on the course of either Raynaud's syndrome or scleroderma. They may cause temporary relaxation of the spasm, but seldom do so if the causative factor is severe and still present Papaverine hydrochloride has only questionable value. The ingestion of alcohol or the use of hot baths for uninvolved extremities to produce reflex vasodilatation is more reliable. Tetraethyl ammonium bromide (Etamon) and Dibenamine have been suggested for these conditions, but the clinical results in patients who have been treated with these drugs have been inconclusive.

Priscoline and Roniacol in doses of 25–50 mg three to five times a day are now widely used and do appear to reduce the attacks in some, but not all, mild cases. Further observations are required for final evaluation.

ACTH and cortisone are being tried for treatment of scleroderma but results with these agents in our hands are thus far unconvincing.

Abstinence from tobacco.—The use of tobacco by patients with Raynaud's syndrome may be contraindicated on the basis of its

be kept warm, because chilling will cause spasm of the vessels and interfere with healing.

Mecholyl ion transfer.—Ion transfer using acetyl-beta-methylcholine chloride (Mecholyl) has been used for some years for Raynaud's syndrome and scleroderma. After approximately 15 years of experience, it must be concluded that it is a palliative for patients with uncomplicated Raynaud's syndrome, sometimes decreasing the frequency and severity of the attacks in mild cases and aiding in the healing of ulcers in more severe cases. It is not a cure and does not prevent attacks under severe provocative conditions such as extreme cold It is useful in helping patients through the winter months when they are forced to stay in a cold climate, but in all probability it does not affect the ultimate course of the disease.

Mecholyl ion transfer also is useful in some cases of scleroderma (see Fig. 52, *C*) Some few patients have shown a remarkable response, but the results in general have been disappointing. Since there is no other form of therapy, conservative or surgical, which affects the long-range course of scleroderma, Mecholyl ion transfer may be advisable in some cases. The treatment has been described by Kovacs

Briefly, the necessary equipment includes: a galvanic machine with a smooth current; malleable electrodes and connecting wires; electrode pads 10 × 12 sq in ; bandages; asbestos paper or cloth; solution of *Mecholyl 0.1–0 25 per cent.*

Special asbestos paper or cloth is dipped in the solution and applied over a severely involved area such as the hands or arms. No holes through this may be left open The malleable electrodes are wrapped around this area and fixed by bandages, making sure that nowhere does the metal come in contact with the skin. The electrodes are then connected with the positive pole of the galvanic machine. The negative electrode pads are moistened in water and placed elsewhere on the body surface, usually on the middle of the back, and connected with the negative pole. The current is very gradually turned on and increased to 15–20 ma. and kept at this level for 30–40 minutes, then gradually

turned off. If the patient complains of a burning sensation, the treatment is discontinued immediately and the electrodes are readjusted.

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ACTH and cortisone are being tried for treatment of scleroderma but results with these agents in our hands are thus far unconvincing.

Abstinence from tobacco—The use of tobacco by patients with Raynaud's syndrome may be contraindicated on the basis of its

vasoconstricting tendency and the probability that the more frequently vasoconstriction occurs in small vessels, the more likely is permanent damage to result. On the other hand, smoking does not appear to have the specific severe aggravating effects on Raynaud's syndrome that it has on thromboangiitis obliterans Until further studies clarify this problem, I recommend that patients with moderate and severe cases stop smoking. Temperature studies of the finger-tips during smoking may disclose patients who are particularly susceptible to tobacco.

SURGERY

It is my purpose to discuss only the general aspects of surgery for Raynaud's syndrome and scleroderma and the results of various methods. Conclusive studies have not been presented regarding some surgical approaches such as ganglionectomy, and new surgical methods may be developed Certain statements may be made at this time

1. No conclusions should be drawn regarding the clinical result until the patient has been followed for a minimum of one year and preferably three years postoperatively. The literature contains numerous reports of little value because based on postoperative check of only one to six months There is often nonspecific improvement, with encouraging change in surface temperature and relief of symptoms, for a few months But the results at the end of a year in the same patient may be entirely negative The disease may, in fact, have progressed and new ulcers may have developed

2. Lumbar ganglionectomy is simpler technically and hence generally more satisfactory than cervical ganglionectomy. However, Raynaud's syndrome occurs many times more frequently in the upper than in the lower extremities. Unsatisfactory results of lumbar ganglionectomy are usually due to the fact that all essential fibers were not resected The evidence suggests that preganglionic

resections are more satisfactory than resections elsewhere, although this point is still debatable.

We have had two patients in whose upper extremities vasospasm developed immediately after lumbar sympathectomy. In one, the typical Raynaud syndrome developed in the hands for the first time. In the second patient, within five hours of a left lumbar sympathectomy the right hand and arm became cold, blanched and extremely painful After a great variety of vasodilators with reflex heat had failed, a stellate block improved the color slightly, but 10 months later she still had a disabled hand not unlike Sudeck's atrophy.

3. In general, the more advanced the condition the less satisfactory the surgical results.

4. Ganglionectomy is, in my experience, futile in the presence of scleroderma of even moderate degree. The patient with the mildest case may receive temporary benefit, but in general the operation is not to be recommended for this type of patient.

5. In patients with associated shoulder girdle syndromes including cervical rib, scalenus anticus, hyperabduction and costoclavicular, when Raynaud's syndrome is progressive Lord, Huebner and I have been investigating exploratory surgery with freeing of pressure and tension points from the nerves and blood vessels in the supra- and postclavicular space. Results cannot yet be evaluated.

6. Parathyroidectomy has been recommended for scleroderma, but a number of patients I have observed a year after this operation have shown no improvement, even though several reported temporary improvement lasting three to six months This operation has largely been abandoned for scleroderma.

With the foregoing facts in mind, one may say that in uncomplicated but progressively severe cases of Raynaud's syndrome properly performed ganglionectomy offers a good chance for relief from attacks and for the comfort of warm extremities at least for several years or more. The fundamental physiologicopathologic process is probably not affected by the procedure, but the nerve

vasoconstricting tendency and the probability that the more frequently vasoconstriction occurs in small vessels, the more likely is permanent damage to result. On the other hand, smoking does not appear to have the specific severe aggravating effects on Raynaud's syndrome that it has on thromboangiitis obliterans. Until further studies clarify this problem, I recommend that patients with moderate and severe cases stop smoking. Temperature studies of the finger-tips during smoking may disclose patients who are particularly susceptible to tobacco

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impulses producing the attacks are blocked and the disagreeable symptoms and sequelae are temporarily controlled. It is not recommended in early cases because in many the disease does not progress. With evidence of progression and increasingly severe symptoms, however, it is not wise to wait until the disease has reached an advanced state with sclerodermatous changes if good results are hoped for. Since the condition usually progresses slowly, the course may be studied for several years One must be aware, however, of the occasional fulminating case which progresses to extreme sclerodermatous involvement within four to six months.

For details of the preferred surgical technics the reader is referred to the excellent summaries of White, Adson and Brown, Craig and Horton, and Pratt, in which the relative merits of different methods of approach are discussed

Hines and Christensen presented some interesting data on the prognosis of Raynaud's disease as it occurs in males. Among 69 cases from their group, sympathectomy was performed in only two, both with improvement, although how long the improvement had been maintained was not mentioned Of the remaining 67 patients, given conservative treatment, 33 per cent had improved to the point of having little or no incapacitation at the time they reported; 44 per cent reported that their condition had remained practically the same or that they were reasonably well The other 23 per cent reported that they were worse at the time of the follow-up than when last seen at Mayo Clinic. Thus 77 per cent enjoyed reasonably good health or at least had not become worse following conservative measures This substantiates the conviction that surgery is indicated only in rapidly progressive cases.

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CHAPTER VII. Essential Polyangiitis (Periarteritis Nodosa; Kussmaul-Maier Disease)

THE TERM "periarteritis nodosa," commonly used for this bizarre symptom complex, is an unfortunate misnomer since vessels of both the arterial and the venous system may be affected, all layers of the vessel walls are involved by the process and in the majority of cases nodules are not present. Any and all blood vessels may be involved and the etiology is unknown. Essential vasculitis would be preferable, though not necessarily the best term. "Essential polyangiitis" is probably most acceptable.

The disease is generally thought to be relatively rare, only about 350 cases having been reported up to 1940, but on the basis of actual clinical demonstration in many army and civilian hospitals I believe that acuity on the part of the clinician and the free use of biopsy technics would make the diagnosis more common Males are much more often affected than females, in contrast with lupus erythematosus disseminatus. It may occur at any age, having been reported from the age of 10 days to 77 years. Approximately 50 per cent of cases occur in the fourth and fifth decades. Mortality has been considered to be extremely high (90–95 per cent), but it is probable that many mild cases are unrecognized and that as diagnosis becomes more acute the mortality rates will be revised

The disease was first reported by Rokitansky (1852) and described in detail by Kussmaul and Maier (1866).

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antisyphilitic arsenicals, thiourea, thiouracil and bacterial infections. Hypersensitivity may ultimately be found to be the fundamental mechanism in a large percentage of, if not all, cases of this syndrome Some such relationship should certainly be sought in each patient. The following case is an example.

The patient received sulfathiazole for three days for a minor local infection. Three weeks later pneumonia developed and he was given

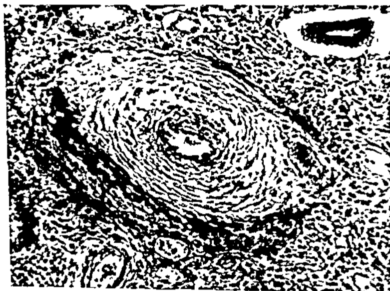


FIG 61—Essential polyangiitis involving small artery of the kidney.

sulfathiazole again, although this clearly was not indicated because the pneumonia was of the primary atypical type. He received 4 Gm. for the first dose and 2 Gm every four hours thereafter. Twenty hours later there developed a diffuse erythematous rash with hives. Therapy was then shifted to sulfadiazine and he was brought to the hospital.

Etiology

The etiology of essential polyangiitis has not been identified However, the work of Rich and others has strongly suggested that the mechanism, at least in some cases, is hypersensitivity and that the precipitating substances may be numerous. In 1942 Rich reported six cases in which the condition developed during serum sickness and sulfonamide therapy. Rich included the report of one patient who had serum sickness and who showed the lesions of essential polyangiitis without having received sulfonamide therapy Death from serum sickness was considered rare prior to 1941. After the sulfonamides came into general use, death of patients who had had serum sickness shortly before death became more frequent, for the reason that the sulfonamides administered with antiserum may prolong life sufficiently to permit serum sickness to develop before the patient dies of the infection. Such were the cases first observed by Rich. The clinical manifestations in these patients were not identical, but included urticaria, lymph node enlargement, maculopapular rash, muscle pain, hematuria, impairment of renal function and hypertension. Histologically lesions in all of the cases were typical of essential polyangiitis.

The possibility that essential polyangiitis was due to hypersensitivity had been suggested by Gruber (1925) and others The presence of eosinophilia is suggestive. Clark and Kaplan (1937) had found the lesions of essential polyangiitis in patients who had developed serum sickness following the administration of serum. Rackemann and Greene, Wilson and Alexander, and others have called attention to the frequent relationship of bronchial asthma and essential polyangiitis Rich and Gregory in 1943 added further evidence concerning the relationship of hypersensitivity to this condition by producing typical lesions in normal rabbits by intravenous injection of a single large dose of foreign protein. Since this aspect of the etiology was presented, reports have been published suggesting a relationship to sulfathiazole alone, iodine,

one, all phases possibly being present at once, which explains the characteristically unpredictable remissions and recrudescences Lesions in the veins are similar to those found in the arteries.

Proposed classifications based on the organs or systems of organs secondarily involved are misleading since each instance is a manifestation of the same process. Chance dictates the part of the vascular tree to be involved. The extent and location of the infarction of any organ determines the pathologic process and hence the symptomatology.

Gruber tabulated the localization of pathologic changes found in 108 cases of the disease (Table 7). Secondary renal and cardiac

TABLE 7—ORGANS INVOLVED IN 108 CASES OF ESSENTIAL POLYANGIITIS

	Times	%		Times	%
Kidneys	80	74	Skin, subcutaneous tissues	14	13
Heart	71	66	Bronchi	9	8
Liver	66	61	Brain	9	8
Stomach, intestines	50	46	Lungs	4	3 7
Mesentery, peritoneum	41	38	Lymph nodes	3	2.7
Musculature	32	30	Bladder, ureters	3	2 7
Pancreas	36	33	Spinal cord	2	1 8
Genitalia	21	19	Thyroid gland	2	1 8
Peripheral nerves	20	18 5	Pleura	2	1 8
Spleen	15	14	Mediastinum	2	1 8
Adrenals	15	14	Sympathetic nervous system	1	0 9
Gallbladder	13	12	Synovial membrane of joints	1	0 9

insufficiency are common causes of death Death has followed profuse hemorrhage resulting from rupture of arterial aneurysms in various vital areas including the brain, lungs, intestines, liver, kidney and pericardium.

Friedberg and Gross presented pathologic evidence of a close relationship between rheumatic fever and the vascular lesions termed *periarteritis nodosa*. They reported four cases in which widespread "periarteritis nodosa" was associated with rheumatic fever and rheumatic heart disease, confirmed by the presence of what they believed to be Aschoff bodies in the myocardium. These were among 13 autopsy cases with essential polyangiitis Two other cases in the series had histories of rheumatism and evidence

lesions were in the kidney, where every glomerulus appeared to be completely replaced by eosinophils. Prolonged search failed to reveal a single glomerulus which appeared capable of functioning.

Pathology

The pathologic picture may be considered under two headings: (1) the vascular lesions characteristic of the disease, and (2) the effects on various organs or portions of the body as a result of interference with their blood supply.

Arkin suggested division of the characteristic changes in the small arteries into four stages. In the *first* or acute stage necrosis occurs in the innermost part of the media of the small arteries, which have no vasa vasorum (the assumption that they have no vasa vasorum is questionable), and in the outer portion of the media of large arteries, which have vasa vasorum. In the *second* or subacute phase there is inflammation with exudate, eosinophils (sometimes in large numbers), lymphocytes, plasma cells and some polymorphonuclear leukocytes are present, and the fixed tissues around the vessels show beginning proliferation. The intima may also proliferate with the occurrence of occlusion of the lumen and infarcts in various organs Aneurysms or nodules may develop at this stage. The *third* or chronic phase is characterized by the appearance of granulation tissue around the arteries and the beginning of healing In the *fourth* phase the lumen is greatly reduced or obliterated and the wall is replaced by scar tissue and periarterial fibrosis. The rate at which nodules appear and disappear in some instances indicates that the change from one phase to another may be quite rapid

Two points require clarification. (1) Only a small segment of an artery may be involved, other portions showing no pathologic changes. (2) Although such a division as Arkin's helps to crystallize the conception of the process, it is not actually sharply divided into four phases. Instead, each blends into the succeeding

one, all phases possibly being present at once, which explains the characteristically unpredictable remissions and recrudescences. Lesions in the veins are similar to those found in the arteries.

Proposed classifications based on the organs or systems of organs secondarily involved are misleading since each instance is a manifestation of the same process Chance dictates the part of the vascular tree to be involved. The extent and location of the infarction of *any organ* determines the pathologic process and hence the symptomatology.

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of rheumatic valvular disease. Verrucous endocarditis was found in both at autopsy. In two cases abdominal operations were performed for symptoms arising from the periarteritis, and the authors suggested that in cases of rheumatic fever abdominal symptoms should call to mind the possibility of essential polyangiitis, even though similar abdominal complaints are encountered in uncomplicated cases of rheumatic fever.

Degenerative changes have been noted in the peripheral nerves and, in view of the incidence of neuritic symptoms, probably would more often be found if carefully searched for. Kernohan and Woltman concluded that these changes are the result of occlusion or marked narrowing of the lumens of the nutrient arteries to the nerves The degeneration, which is diffuse at the lower levels, begins as an infarction proximally. The infarcts may be single, multiple or confluent and may involve several nerve bundles. These authors found no inflammation in any of the nerves studied

Eosinophilia.—Careful studies of the blood smears frequently reveal definite eosinophilia This may range from 10 to 70 per cent or more and it has been found in 15–50 per cent of the cases of essential polyangiitis reported in different series. This may be related to the observation of Baehr and Pollack that eosinophilia is usually pronounced in the early stages although it may be absent in the later, healing phases.

Clinical Manifestations

The fundamental clinical observation regarding essential polyangiitis is its bizarre picture which may resemble an almost unlimited variety of diseases. The average duration is a few weeks to five months. However, it has been reported as fatal within four hours of the onset of symptoms, and patients have lived for several years after a biopsy diagnosis. The pathologic process was probably present longer than was apparent in the case of brief duration The symptoms are so confusing that the diagnosis frequently is not made during life. The syndrome usually appears as a fairly

acute or chronic sepsis with varied local manifestations. The general clinical manifestations most often noted are irregular low grade fever, sweating, weakness, loss of weight, prostration, anemia, dyspnea, tachycardia, muscular, neuritic and abdominal pains and hypertension.

The symptoms manifesting secondary local involvement are almost limitless in number and variety. For example, neuritis results from infarction of the peripheral nerves, albuminuria and hematuria from renal infarction, diabetes from involvement of the arteries of the pancreas, intestinal hemorrhage and colic from necrosis of the intestinal mucous membrane secondary to involvement of the [illegible]

[illegible]

and is sometimes accompanied by extraordinary changes in the electrocardiogram. The list might be prolonged indefinitely.

Meyer described a triad of syndromes which he considered characteristic: (1) chlorotic marasmus (of Kussmaul and Maier), (2) polymyositis and polyneuritis, and (3) gastrointestinal disturbances, including cramps, colic, tenderness, signs of peritoneal irritation, anorexia, vomiting, diarrhea or constipation and gastrointestinal bleeding. A fourth cardinal syndrome—the nephritic—was emphasized by Brinkmann and by Christeller It may be characterized by albuminuria and hematuria, edema, nitrogen retention of the blood, retinitis and edema of the disks and retinas and elevated blood pressure, which may also be due to widespread arterial involvement Hypertension has been reported in about 30 per cent of all cases.

Three types of skin and subcutaneous tissue changes have been noted: rash, edema and subcutaneous nodules (Rothstein and Welt). The rashes have been hemorrhagic, varying from petechial spots to necrotic ulcerations, or erythematous Edema, either generalized or limited to the face or the hands and feet, has frequently been reported It is usually considered to be of nephritic origin

The subcutaneous nodules represent sacculations (aneurysms) or thickening in the walls of the arteries. They are small, firm, pea-sized, shotlike masses lying along the artery and usually are quite superficial and painless but may be reddened and tender; occasionally suppurative degeneration takes place. These nodules, occurring in one in eight cases, aid in the clinical diagnosis and may permit a positive diagnosis on biopsy study.

Pains in the joints may be severe enough to simulate acute rheumatic fever, especially when several joints are involved Lamb noted joint pains in 39 per cent of his series. This symptom, together with myositis, neuritis and sore throat, suggests a relationship to a rheumatic or arthritic syndrome. Salicylates do not influence the symptoms or course.

The abdominal symptoms may be so severe as to simulate an acute surgical condition, and operations have been performed in reported cases on the basis of preoperative diagnoses of acute appendicitis, cholecystitis, cholelithiasis and various nephritic and perinephritic conditions. In these cases essential polyangiitis was diagnosed either at operation or at autopsy, when massive hemorrhage has often been found secondary to ruptured aneurysms of branches of the cystic, mesenteric or hepatic arterial trees

Gangrene of a lower extremity in some cases has necessitated amputation, followed by histologic confirmation of the diagnosis. It is rather unusual to find several of these syndromes active at one time, the more typical picture being one of successive exacerbations [illegible] ptoms in [illegible] patients [illegible] neralized symptoms predominating until death occurs

DIAGNOSIS

The most important factor in the recognition of essential polyangiitis is the physician's awareness of the existence of the disease

and its vagaries. The extent of potential organic involvement has resulted in its confusion with a great number of diseases, including trichinosis, myositis, purpura haemorrhagica, abscess of the liver, typhoid and paratyphoid fever, amebiasis, brain tumor, cholecystitis, various nephritic and perinephritic conditions, miliary tuberculosis, meningitis, alcoholic polyneuritis, lead neuritis and gastroenteritis. The relation of essential polyangiitis to lupus erythematosus disseminatus and scleroderma has been the subject of much study in recent years. Klemperer and others have suggested that they might well be grouped together with rheumatic fever under the general heading of diffuse collagenous diseases. In any case of a prolonged, unexplained fever the diagnosis of polyangiitis must be seriously considered along with Hodgkin's disease, lupus and subacute bacterial endocarditis.

The only significant laboratory finding is eosinophilia, which is characteristic when present (15–50 per cent of cases) but is not specific for the disease. Differentiation from other conditions may prove difficult and be solved only by elimination, providing a tentative diagnosis, or by biopsy or postmortem examination.

Treatment and Prevention

The situation regarding treatment has changed somewhat since the advent of ACTH and cortisone. Experimentally, remissions of polyangiitis have been reported. It is difficult to evaluate these observations since the disease is typically prone to remissions. However, this approach has seemed encouraging and, indeed, cases have remained arrested for long periods after the use of these drugs. Further studies are in progress in several hospitals

Symptomatic treatment should, of course, be used. This must of necessity be extremely varied and is often unsatisfactory. The judicious use of sedative and vasorelaxing drugs such as papaverine and Pantopon may be attempted, but they are probably of value only for the relief of pain and apprehension. Arsenicals have been used,

but there is no satisfactory evidence of their efficacy. The sulfonamides and antibiotics have proved of no value.

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CHAPTER VIII· Cranial Arteritis (Temporal Arteritis)

ARTERITIS PRIMARILY of the temporal vessels was first described by Jonathan Hutchinson in 1890, but no other cases were reported until Horton, McGrath and Brown described theirs in 1932. Between 1932 and 1944, 36 cases were observed at the Mayo Clinic and cases have been reported in the literature by others. It is probable, however, that the syndrome is much more common than the literature indicates, for I have observed 12 cases in consultation, none of which have been reported, and other students of peripheral vascular disease have had a similar experience.

Cranial arteritis is a febrile, self-limited disease of variable duration and unknown etiology which always involves the temporal arteries and occasionally also involves other arteries in the cranial system. It occurs in the older age groups, few cases having been seen or reported in persons under 55. It seems to have no predilection for one sex and has no seasonal incidence.

ETIOLOGY

The general reaction plus the local disturbance suggest that we are dealing with a generalized, debilitating, subacute disease probably of low grade infectious nature. Although it has been observed largely in persons of the older age group, pathologic findings have been noteworthy for absence of atheromatous plaques in the involved arteries. The possibility of an allergic reaction has been

considered, but Stillborn and Wolff pointed out that (1) the rarity of eosinophilia, (2) the advanced age of the patients and (3) the localization of the arteritis are against this theory. The relatively high incidence of concomitant or preceding oral infection was thought suggestive, but the evidence in this regard is certainly inconclusive. The question has repeatedly been asked whether this is the same disease as essential polyangiitis The available evidence is against this view.

PATHOLOGY

The large temporal arteries are observed as tortuous, swollen, nodular vessels with or without pulsation and with cellulitis of the surrounding tissue. The facial, carotid, occipital, cerebral and retinal vessels may be involved.

Microscopic examination of the temporal artery has uniformly revealed a panarteritis not readily distinguished from essential polyangiitis (Fig 62). There are hypertrophy of the intima and medial necrosis associated with granulomatous tissue and, in some instances, foreign body giant cells, periarterial cellular infiltration and thrombus formation. Eosinophilic lesions are rare but have been reported.

SYMPTOMS

The local symptoms include pain and tenderness in the region of one or both temporal arteries. Pain has also been reported in the jaw, occipital region and elsewhere on the side of the head and face. The involved temporal arteries are usually reddened, swollen and thickened. At first pulsations may be present, but later thrombosis takes place and pulsations may no longer be felt. Nodules or extensive indurations are occasionally palpable. Frequently there is a generalized pain which appears to be intracranial, and half of the patients suffer pain on mastication. An increasing number of patients are reported to have partial or com-

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plete loss of vision as a result of cranial arteritis. Diplopia and photophobia have also been noted. In a case reported by Shannon and Solomon bilateral complete loss of vision was believed due to the fact that the retinal artery had become the site of a pathologic process similar to the one observed in the temporal artery.



FIG 62 —Cranial arteritis Typical section from involved temporal artery

Mental sluggishness, dizziness, vomiting, dysarthria, delirium and even coma have been described, and some patients appear never to recover completely from lethargy or mental deterioration. Generalized symptoms characteristic of the syndrome include weight loss, which may be up to 30 or 40 lb., fever, anorexia, general malaise, sweating and weakness. The fever may average 100–104 F. and may persist a long time, as in one patient I ob-

served who had fever for 13 months. Pain has been reported along the course of brachial and radial arteries and in the thighs, knees and ankles, although it is entirely possible that such cases really are examples of essential polyangiitis rather than of cranial arteritis

Results of laboratory studies have not been very specific. Leukocyte values of 7,500–15,000, with some increase in the proportion of polymorphonuclear cells, are common. Eosinophilia is characteristically absent, in contrast with essential polyangiitis. Bacteriologic studies have been disappointing. Various workers have isolated actinomycetes, streptococci, Staphylococcus aureus and other organisms, but there has been no constant bacteriologic finding and none of the postulates of Koch have been fulfilled.

The following differences between essential polyangiitis and temporal arteritis are apparent.

Essential Polyangiitis	Cranial Arteritis
May occur at any age, even infancy	All patients previously reported, over 55
Generalized involvement, often with serial involvement of one set of vessels of body after another; veins may be involved	Sharply localized to temporal arteries and arteries of head closely associated with temporal arteries
Involvement of temporal arteries alone extremely rare at any phase	Temporal arteries always involved
Eosinophilia in 15–50%	Eosinophilia absent or very rare
Usually, but not invariably, fatal	Prognosis good; no reported fatalities, but several cases of permanent blindness

Treatment

Without treatment the pain and other manifestations tend eventually to subside, with permanent cure. Of the 12 patients I have seen, the six with the most severe symptoms have had excision of the involved temporal artery or arteries. Five of the six received almost dramatic relief within 24 hours postoperatively, although pain in the temporal arteries had been present in some for a number of months. The sixth patient complained of

severe intracranial headache believed to be due to the involvement of intracranial vessels.

The simple procedure of excision of the involved temporal arteries is advisable in all cases in which pain is severe. Although pain is usually relieved, the general manifestations of the disease will not necessarily subside following excision of the temporal arteries. One patient in whom the temporal arteries were excised had complete relief from pain, but fever, malaise, weakness and loss of weight persisted for 13 months, followed by complete recovery

Roberts and Askey have reported relief from the pain and headaches of cranial arteritis following the periarterial injection of 1 per cent procaine hydrochloride. In some cases it was necessary to repeat the injections on several days.

No other form of treatment has been demonstrated to be of any value The usual drugs—salicylates, codeine and papaverine—may be tried for the relief of pain, despite their frequent failure. Because the course is frequently relatively long, the injudicious use of narcotics must be avoided.

Through the courtesy of Lawrence Meyers and Jere W. Lord, Jr , the following case is included.* It is instructive in that it includes most of the common features but has the added interest of being in one of the youngest, if not the youngest, patients on record and in presenting certain unusual pathologic findings, notably profound periarteritis.

A housewife aged 22 was admitted to the New York Post-Graduate Hospital in December, 1945, with the chief complaint of left-sided temporal headaches of three months' duration. Although she had experienced mild intermittent left-sided headaches for a year, in September, 1945, the pain became sharply localized to the left temporal region and was associated with deep-seated retrobulbar discomfort. The patient felt a throbbing sensation and tenderness in the temporal region. In addition there were mild general symptoms of chilliness, fever, malaise

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and weakness Physical examination at that time gave essentially negative results except in the left temporal area, where the temporal artery was discovered to be thickened, beaded and tender and showed a feeble pulsation. The skin overlying it was reddened. The artery was involved for 4 cm (Fig 63). The general symptoms cleared in a few days and the local manifestations in three weeks. During the next two months the patient was troubled only by mild intermittent left-sided temporal headaches. Results of an ophthalmologic examination by Dr. Rudolf Aebli at this time were negative. Three weeks before hospitalization the local symptoms and signs recurred with great intensity but without any of the constitutional symptoms.

Examination on admission showed the left temporal artery to be thickened, beaded and tender and a faint pulsation was palpable. The skin overlying the artery was not reddened Examination of the other arteries of the scalp and extremities gave negative results. Temperature, white blood cell count, sedimentation rate and urine were normal. On December 22, under local anesthesia, the entire involved segment of the left temporal artery was removed. Immediately the headache and retrobulbar discomfort subsided. Dr. A. E. Margulis, of the Department of Pathology, examined the specimen ...

... The vessel wall seems slightly thickened but is still pliable and around the vessel is a cuff of fibromuscular connective tissue

"Microscopic: This artery was cut serially from end to end and studied in hematoxylin-eosin, trichrome, elastica, van Gieson's and Gram's stains. The vessel shows both periarteritis and arteritis. The most striking change is the periarteritis. This appears as an eccentric cap in the perivascular tissues, surrounding one-third to one-half the perimeter of the vessel, and invades the surrounding fibrous and muscle tissue The lesion extends for a considerable distance in the long axis of the artery and probably accounts for the nodularity before excision. This periarterial inflammation is an area of granulation tissue, with numerous small caliber, thin- and thick-walled vessels in an area of delicate fibrosis infiltrated by lymphocytes ...

... hemosiderin pigment No giant cells are seen

"The changes in the vessels involve all coats and are proliferative and

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fibroblastic rather than exudative. The intima is much thickened in irregular fashion so that the luminal surface is scalloped; the lumen is much reduced in caliber but nowhere obliterated or filled with thrombus. The thickening of the intima is by a generally loose, finely fibrillar connective tissue in which are found occasional groups of smooth muscle cells The luminal surface is covered by an intact layer of slightly swollen endothelial cells The internal elastica shows focal changes. There are areas of degeneration where it stains poorly and is very finely crenated, and areas where it is completely absent, at the margins of such areas shadows of elastic fibers being noted. The muscular coat shows principally focal atrophy, areas of partial disappearance of the muscle fibers by a finely fibrillar fibrosis. No giant cells are noted in any coats of the vessels. Bacteria are not demonstrated either in the wall of the vessel or in the perivascular inflammation (Fig 64)

"Diagnosis: Periarteritis and arteritis of segment of temporal artery

"Note The changes described do not conform precisely to the histologic changes reputed to occur in the syndrome of temporal arteritis More specifically there is not the exudative giant cell arteritis which has been found in the active phases of this syndrome. It must be emphasized, however, that not all the biopsies or autopsies performed in this disease have shown such giant cell arteritis. Relatively few histologic studies have been made, and it is doubtful that the complete life cycle of this lesion has been delineated. Clinically it is known that the lesion regresses and that the artery apparently returns to normal, but not much is known about the histologic structure of the healing or late stages."

The patient was seen at frequent intervals for 12 months postoperatively and had remained entirely free from headache and retrobulbar pain The operative site remained well healed and the proximal normal left temporal artery was compressible, nontender and pulsated normally

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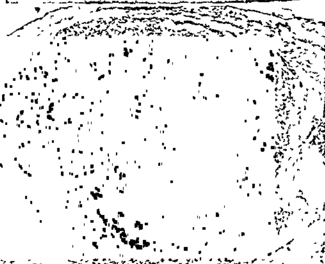


FIG. 63 *(above)* —Cranial arteritis. Swollen, inflamed segment of anterior branch of left temporal artery, with process extending 3 cm beyond the hair line

FIG. 64 *(below)* —Cranial arteritis (same case as preceding). Cross-section of resected temporal artery, showing most pronounced inflammatory changes in the perivascular region (Figures 63 and 64 from Meyers, L., and Lord, J. W., Jr. J.A.M.A. 136:169-171, Jan. 17, 1948; reproduced with permission.)

rucous endocarditis," which is related to lupus erythematosus disseminatus Since 1924 numerous papers have appeared which described the disease from the clinical and pathologic standpoints.

Etiology

The etiology is unknown. Early theories of its relation to tuberculosis have been discarded. The disease may appear at any age, although most of the patients reported on have been in early adulthood and middle age Females are much more frequently affected than males. At present it is fashionable to consider this, along with numerous other diseases, as an allergic response to an unknown agent, but the evidence with reference to lupus erythe matosus is too limited to justify acceptance at this time.

Pathology

In 1941 Klemperer, Pollack and Baehr and their co-workers first called attention to the fact that these lesions were local expressions of a morbid process affecting the entire collagenous tissue system. The most prominent alteration is fibrinoid degeneration. There are thickening and straightening of the collagen fibers, which are more friable than usual. There are marked eosinophilia and refractibility. There is a visible increase in the ground substance All these changes are due to a profound physicochemical aberration of the colloid state of the connective tissues.

In Libman and Sacks's four cases (1924) endocardial lesions were described as atypical verrucous endocarditis Clinical signs included fever, progressive anemia, pericarditis, arthritis, white-centered petechiae, erythematous purpuric rashes, ulcerative lesions of the mucous membranes, pleural and pulmonary symptoms, multiple embolic phenomena, enlargement of the liver and spleen, acute glomerular nephritis, a tendency to leukopenia and repeatedly negative blood cultures Two of the four patients had an eruption of the face resembling lupus erythematosus dissemi-

CHAPTER IX · Lupus Erythematosus Disseminatus

BEFORE WE ENTER on a discussion of lupus erythematosus it is essential to consider the most recent theories regarding its relationship with scleroderma and similar diseases Klemperer, Pollack and Baehr and others have found that certain diseases affect the connective tissue system throughout the body and might be called diffuse collagen diseases Misinterpretation gave rise to the erroneous impression that the diseases themselves are necessarily related. Klemperer and his co-workers have been quite specific on this point: ". . . to identify this system as the seat of certain diseases is by no means to identify these diseases with one another, or even to relate them This would be an unjustifiable oversimplification."

In 1845 Hebra first described lupus erythematosus as a cutaneous disease usually of localized nature. He used the term "seborrhea congestiva." Six years later Cazenave gave the disease its present name. In 1872 Kaposi pointed out that the disease sometimes had generalized systemic reactions and was at times responsible for death. Three of his 11 patients died while under his observation In 1895 Osler described a group of cases in a paper entitled "On the visceral complications of erythema exudativum multiforme," and in 1924 Libman and Sacks described the development of mural and valvular endocarditis or "atypical ver-

the capillary bed in certain areas, as in the skin, with bloody and serous extravasations, perforative lesions of the endothelial linings of the capillaries, arterioles and venules associated with thrombi which often obstructed or occluded the lumens and degenerative and necrotizing lesions in the walls of these vessels associated with thrombosis and sometimes with hemorrhages in the adjacent tissues.

Glomerular changes consisting of perforative and thrombotic lesions of the capillary loops have often been observed. It was thought at one time that a peculiar hilar thickening of the capillary walls, termed the "wire loop lesion," was specific for the disease, but that is not the case. It is, however, typical of the disease.

Although there has been a considerable discussion as to whether so-called Libman-Sacks disease is the same as lupus erythematosus, the general inclination seems to be to consider the two conditions different manifestations of the same syndrome. This subject is appropriately included in a book on peripheral vascular disease because of the high incidence of blood vessel involvement, usually of the smaller radicles. Fibrinoid degeneration involving the adventitia of the blood vessel walls is common and often widespread Periarterial fibrosis in an "onion skin arrangement" is often found involving the smaller arterioles, particularly those of the spleen. And not infrequently there is an involvement of the blood vessel walls resembling the changes seen in essential polyarteritis.

There are no serologic or skin tests which aid in the establishment of the diagnosis. A false positive Wassermann serum reaction may be present during an exacerbation of disseminated lupus erythematosus A biopsy of the skin lesion, when present, and the autopsy findings are the sources of positive information. Cells alleged to be quite specific for lupus have been described by Hargraves and by Montgomery and McCreight and others. They are found most easily in the sternal bone marrow.

natus. Autopsy revealed verrucous endocardial vegetations whose structure differed from that of rheumatic and subacute bacterial endocarditis. The lesions contained no bacteria Aschoff bodies and Bracht-Waechter lesions were not found. In two cases there was diffuse glomerular nephritis, in three pleuritis, in two broncho

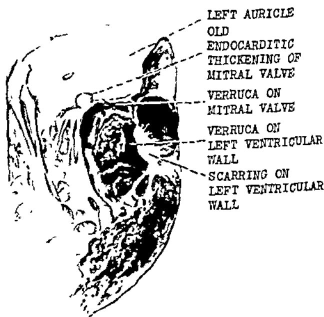


Fig 65 —Lupus erythematosus disseminatus Drawing showing verrucous involvement of heart (Courtesy of Dr Teresa McGovern.)

pneumonia, in one ascites and in three enlargement of the spleen with small splenic infarcts.

Post described in detail the cardiac changes in 11 cases of atypical verrucous endocarditis. Five of the patients, all females, had erythematous eruptions resembling acute lupus erythematosus. Microscopic study revealed remarkable vascular lesions extending throughout the finer ramifications of the systemic and sometimes the pulmonary circulation. They consisted of simple dilatation of

globulin values were above 2.5 Gm. and in 2 cases below this amount. Reactions to serologic tests for syphilis were negative in all cases. Abnormal urinary values, including albuminuria, pus and casts, were found in 14 of 17 cases.

The nondisseminated cutaneous lesion, commonly termed chronic discoid lupus erythematosus, is the usual form of eruption. Although common on the face, in typical butterfly pattern, it may appear elsewhere There is an erythematous scaling appearance which becomes increasingly red or fades out in a few days. The individual lesion begins as a small red macule in a slightly raised edematous area which spreads peripherally. It is later covered with adherent grayish scales. Frequently patulous or wide-mouthed follicles and follicular plugs are seen. Telangiectasia is common. Late in the disease the skin becomes atrophic. The course progresses through the stages of increased follicular openings with telangiectasia over a period of years. Sometimes the lesions appear to be more of an urticarial nature. There is a resemblance to psoriasis or lichen planus, and in some cases there is a hyperkeratotic discoid appearance with a grayish depressed area centrally.

This dermatologic description is included here because these skin lesions frequently blossom forth into a widespread disseminating process with a fatal ending Since acute disseminating lupus erythematosus is almost invariably fatal, its recognition is of great prognostic importance. It should be noted that occasionally a false positive Wassermann reaction is obtained.

As is the case with many other diseases involving the blood vessels and other widespread systems, chance determines the area affected and hence the predominant symptoms. It is necessary to emphasize that not infrequently the manifestations of the disease are confined to the internal organs, cutaneous involvement not being apparent until relatively late in the course. Such a case was seen in 1944

A nurse in an Army hospital had suffered for nearly a year from intermittent fever, weakness and loss of 35 lb. She complained of vague

Clinical Manifestations

The course of lupus erythematosus disseminatus may vary from a relatively acute development with early death to a subacute or even chronic course lasting one or more years Some patients with unusually chronic cases have lived more than five years In acute cases high fever and a rapidly progressive downhill course are common In chronic cases relapses may alternate with remissions of variable extent

The common clinical features include fever, tachycardia, prostration, weight loss and weakness, with leukopenia, anemia and thrombopenia The urine may contain albumin, casts and blood. Hemorrhagic phenomena such as extensive purpura or petechial spots and bleeding from the mucous membranes are not uncommon Retinal changes in the form of rather typical perivascular hemorrhages or fluffy exudates are often seen. Serous membrane manifestations include pleurisy, pericarditis and ascites. The joints are often involved. The lymph nodes may be swollen and tender. The spleen may be enlarged and abdominal complaints are usual

In 18 cases seen at autopsy, reported by Griffith and Vural, the symptoms and signs encountered were tachycardia over 100 in 18; dyspnea in 16; joint pains in 13, butterfly rash in 11, ankle edema in 6, cough in 6; chest pain in 4, nausea and vomiting in 3, congestive heart failure with hepatosplenomegaly in 3; vaginal bleeding in 2; pericardial effusions in 2, epistaxis in 1. Broncho- or lobar pneumonia was the terminal event in 13 cases. Nine of 12 patients who had electrocardiographic study showed abnormalities, but no characteristic pattern was found

Laboratory studies showed hypochromic anemia in 17 cases In six the erythrocyte counts were between 2,200,000 and 3,000,000 per cu. mm. Fourteen patients had leukopenia. In four the count was normal or moderately elevated. Sedimentation rates were elevated in all five patients in whom it was determined. In two of 13 cases the total protein values were below 5 Gm. In 9 of 13 the

globulin values were above 2.5 Gm. and in 2 cases below this amount. Reactions to serologic tests for syphilis were negative in all cases. Abnormal urinary values, including albuminuria, pus and casts, were found in 14 of 17 cases.

The nondisseminated cutaneous lesion, commonly termed chronic discoid lupus erythematosus, is the usual form of eruption. Although common on the face, in typical butterfly pattern, it may appear elsewhere. There is an erythematous scaling appearance which becomes increasingly red or fades out in a few days. The individual lesion begins as a small red macule in a slightly raised edematous area which spreads peripherally. It is later covered with adherent grayish scales. Frequently patulous or wide-mouthed follicles and follicular plugs are seen. Telangiectasia is common. Late in the disease the skin becomes atrophic. The course progresses through the stages of increased follicular openings with telangiectasia over a period of years. Sometimes the lesions appear to be more of an urticarial nature. There is a resemblance to psoriasis or lichen planus, and in some cases there is a hyperkeratotic discoid appearance with a grayish depressed area centrally.

This dermatologic description is included here because these skin lesions frequently blossom forth into a widespread disseminating process with a fatal ending Since acute disseminating lupus erythematosus is almost invariably fatal, *its recognition is of great* prognostic importance. It should be noted that occasionally a false positive Wassermann reaction is obtained.

As is the case with many other diseases involving the blood vessels and other widespread systems, chance determines the area affected and hence the predominant symptoms. It is necessary to emphasize that not infrequently the manifestations of the disease are confined to the internal organs, cutaneous involvement not being apparent until relatively late in the course Such a case was seen in 1944

A nurse in an Army hospital had suffered for nearly a year from intermittent fever, weakness and loss of 35 lb She complained of vague

pains scattered throughout the body. The urine on numerous occasions had contained albumin and a few casts. Red cells were usually present in small numbers. Several months before I saw her she had complained of gastric symptoms, but these had subsided. There had been some debate among her physicians as to whether a cardiac murmur of organic significance had been heard. A presystolic murmur over the mitral area had been described by some, but was denied by other examiners. The temperature was of septic type, the peaks each day ranging from 101.5 to 103 F. Diagnosis with certainty had been impossible. Essential polyangiitis and lupus erythematosus disseminatus were considered, and Hodgkin's disease was thought likely. On the morning I saw this patient she conveniently produced a perfect butterfly rash over the cheeks and across the saddle of the nose. This was the first rash she had had and it clarified the diagno[illegible] In more typical cases [illegible] is, naturally, of great [illegible].

Exposure to sunlight or ultraviolet light was formerly used in treatment of the skin lesions until it was noted in numerous patients that dissemination followed extensive exposure to the sun. Dissemination has also been noted to follow acute infections, surgical procedures and other incidents which disturb the over-all balance of the patient's physiologic function in one way or another. No doubt in some instances dissemination has been coincidental.

Treatment

As in many other diseases, so too in lupus the advent of ACTH and cortisone has opened the possibility of therapy. Remissions have repeatedly followed closely the administration of these substances, and my experience confirms the belief of others that this has been more than coincidental. In a few patients these remissions have been more complete and more lasting than those previously observed in patients from very advanced states.

For example, a young woman was seen who had been demonstrated by biopsy to have steadily disseminating lupus for two years. Without appreciable remissions she had run a fever, had developed a diastolic apical murmur, and accumulations of fluid in the right side of the chest





FIG 66 *(above)*—Lupus erythematosus disseminatus Typical butterfly rash extended over bridge of nose, laterally on the cheeks and up to forehead (Courtesy of Dr George M Lewis)

FIG 67 *(below)*—Lupus erythematosus disseminatus, with ulceration of scalp (Courtesy of Dr Gilbert Marquardt.)

and abdomen Following the administration of 25 mg. of ACTH four times a day the fever promptly subsided, the fluid cleared from the chest and abdomen and a general feeling of well being returned Her butterfly rash disappeared She has been maintained on Cortone (25 mg orally) for 30 months without a relapse.

It must be noted that even temporary remissions are not universal with ACTH and cortisone therapy. In many patients the temporary improvement is not maintained.

Furthermore, the therapy is not without risk Whenever one administers these drugs untoward effects must be watched for. Among the most common are (1) development of the so-called "moon-face," a rounding out of the facial contours; (2) retention of salt, with gain in weight due to edema; (3) increase in the blood pressure to hypertensive levels; (4) albuminuria and other urinary abnormalities, with aggravation of these if already present, (5) mental disorientation; (6) convulsive states, with death in some instances. The last has been encountered especially in patients with disseminated lupus

Although most of the complications of ACTH and cortisone therapy are reversible on reduction or discontinuance of the substance, the convulsive state may be irreversible. Therefore, we must conclude that although ACTH and cortisone may offer advantages not previously available to these patients, they cannot be administered without very serious thought and meticulous observation

Treatment otherwise is symptomatic, and includes rest and even hospitalization if necessary to secure proper nursing care Exposure to sunlight must be avoided. Supportive treatment should include transfusions and vitamin therapy. Gold, bismuth and iodine have been used, but their value is doubtful.

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When a true cervical rib or elongated transverse process is present x-ray diagnosis is fairly simple. When a nonradiopaque tendon or cartilaginous band is producing the pressure diagnosis becomes increasingly difficult.

The work of J. B. Murphy and later of Adson and Coffey focused attention on the role of the scalenus anticus muscle in the production of neurovascular symptomatology of the shoulder girdle and also on the fact that division of the muscle might in many cases relieve the symptoms and signs. Adson and Coffey demonstrated compression of the subclavian artery by the scalenus anticus muscle against the lower and middle trunks of the brachial plexus as they lie on the cervical rib. There is also a tendency to pinching between the anterior and the medial and minimal scalenus muscles above their points of attachment to the first rib The importance of the cervical rib has decreased in medical thought except in certain definite cases and the significance of the scalenus anticus syndrome has increased.

Naffziger and Grant collected from the literature 51 cases up to 1938 in which symptoms of cervical rib were present but in which the anomaly was not found Haven in 1939 reviewed the chest x-rays of 5,000 patients and found abnormalities of the first thoracic rib in 38 patients (0.76 per cent). Thirty patients (0 74 per cent) had cervical ribs, none with symptoms. Only two of the patients with abnormalities of the first thoracic rib had symptoms referable to the abnormality. One showed definite obliteration of the subclavian artery in a certain position Scalenotomy resulted in marked improvement. In the second there was definite paresthesia of the arm, and the anterior two thirds of the malformed first rib were resected to free the plexus of torsion and tension with good results

Cervical ribs that produce significant clinical findings are certainly infrequent. Adson and Coffey in 1927 reviewed the records of 540,413 patients registered at the Mayo Clinic and found only 303 in which a diagnosis of cervical rib had been made, an inci-

CHAPTER X Neurovascular Syndromes of the Shoulder Girdle

THERE ARE at least four general types of anatomic derangement of the shoulder girdle which may be responsible for neurovascular syndromes involving the upper extremities These, in order of their recognition and description, are (1) the cervical rib syndrome, (2) the scalenus anticus syndrome, (3) the costoclavicular syndrome, and (4) the hyperabduction syndrome.

CERVICAL RIB AND SCALENUS ANTICUS SYNDROMES

Galen and Vesalius were cognizant of the presence of cervical ribs. Careful anatomic studies revealed that the symptoms of the cervical rib syndrome arose from extensions of the transverse processes, or cervical ribs, arising from the seventh, sixth or, rarely, the fifth cervical vertebra. It was later demonstrated that the symptoms might be produced by fibrous or cartilaginous bands in the absence of an actual rib structure with a calcium composition. In 1743 Hunauld described the present concept of this pathologic entity. In 1861 Coote performed an operation for a cervical rib syndrome with relief of symptoms. Since the work of these early investigators it has been recognized that a supernumerary rib or a band in the cervical area might be responsible for pressure on the subclavian artery and brachial plexus which in turn might cause paresthesias, coldness, impairment of circulation and even gangrene of the fingers.

of the neck. These movements caused pinching of the vessels and the plexus between the anterior surface of the first rib and the posterior surface of the clavicle. They found a number of soldiers who, during the war, were forced to carry heavy packs which produced downward and backward displacement of the shoulders. They also demonstrated that this pinching, which in some soldiers resulted in obliteration of the pulses and caused neurologic symptoms, may be reproduced in many normal individuals. Twenty-five of 50 men and 30 of 50 women could obliterate their pulses by forcing their shoulders into the position described. In most persons avoidance of the position will eliminate the condition. In a few it persists

If the shoulder musculature cannot be strengthened to the point where protection is given by a more normal relationship of the structures, surgery with section or establishment of a groove in the anterior surface of the first rib or removal of the rib or clavicle must be considered. The abnormal anatomic relationships may be present without causing symptoms, but in other circumstances may produce a condition which heretofore has been loosely classified as a "scalenus anticus syndrome."

Hyperabduction Syndrome (Wright, 1945)

For many years my attention has been focused by patients on complaints of paresthesias, numbness and tingling after sleeping or working with their arms in the position of hyperabduction Hyperabduction is here used to mean that phase of circumduction which brings the arms together above the head with the elbows flexed or with the plane of their long axes corresponding to that of the body (Fig. 68). Some degree of external rotation is necessary to achieve this position Actually this term, though accepted in anatomic terminology, is not ideal or entirely logical, for abduction is movement away from the median plane of the body and beyond the 90 degree angle, the arm in so-called hyperabduction actually again approaches the median plane. Other terms are, however,

dence of 0 056 per cent In 55 per cent cervical rib was an accidental discovery and did not produce symptoms In only 36 of the 303 patients was surgery warranted.

It has long been noted that the cervical rib-scalenus anticus syndrome occurs with increasing frequency in middle and late adult life. Ochsner, Gage and DeBakey have suggested that contraction and spasm of the scalenus anticus muscle cause abnormal elevation of the first thoracic rib The contraction and spasm are presumed to result from irritation and stimulation of the brachial plexus, some fibers of which supply the scalenus muscles Abnormal elevation of the first thoracic rib causes greater irritation and stimulation of the brachial plexus, establishing a vicious cycle

Another line of reasoning, suggested by the work of Todd, represents what is probably the more common situation. As individuals grow older the muscles normally responsible for holding the clavicle up away from the first rib relax, allowing the clavicle to settle down against the first rib, thus pinching the subclavian axillary artery and brachial plexus. The scalenus muscles tend to hold the first rib in place and may not relax concurrently in some patients. This costoclavicular syndrome is reviewed briefly in later paragraphs Section of the scalenus muscle permits the first rib to drop away from the clavicle and relieve the pinching and torsion of the nerves and vessels between the clavicle and the first rib.

There has been an increasing tendency to sever the scalenus anticus muscle, even in the presence of a cervical rib, in the hope that discomfort might be relieved. In some instances this has happened. Too frequently, however, inaccurate analysis of the condition before surgery has led to inadequate exploratory procedures and unsatisfactory results.

Costoclavicular Syndrome (Falconer–Weddell, 1943)

In 1943 Falconer and Weddell further clarified the picture in the shoulder girdle by describing the syndrome produced by holding the shoulders backward and downward or by hyperextension

ough study of the incidence of this phenomenon in normal persons and of the mechanism responsible for it was not made.

Following some years of study regarding this interesting syndrome I described the neurovascular syndrome produced by hyperabduction of the arms. The first case reported is presented here.

A man, 37, first seen in July, 1939, had superficial gangrene of the [illegible]

numbness and paresthesias of the fingers four months previously. These became more pronounced and extended up the hands and arms. When superficial gangrene appeared at the finger-tips he consulted a physician. No etiologic factors could be found except possibly the smoking of 10 cigarets a day. Roentgenograms showed no cervical ribs

The possibility of thromboangiitis obliterans and of Raynaud's syndrome had been considered by the physician, but there were certain objections to both. The following points were against a diagnosis of thromboangiitis obliterans (1) Pain and tenderness were much milder than is usual in this disease. (2) The gangrenous areas were the atrophic dry type and were not surrounded by angry-looking tissue. (3) The typical color changes of rubor on dependency and pallor on elevation were not present. (4) The ulnar pulses were normal bilaterally. (5) The Allen test disclosed satisfactory function of the vessels of the hands. (6) Cessation of smoking had no effect on the course Against a diagnosis of Raynaud's syndrome was the complete absence of characteristic precipitation of attacks by cold, emotion, trauma or other possible factors There was no history of taking ergot.

I was able to confirm all these observations In addition, roentgen study of the vessels of the upper and lower extremities failed to show evidence of calcification The blood Wassermann reaction was negative. The blood count, nonprotein nitrogen and sugar values and urine were all normal. Oscillometric readings with the patient supine with his arms by his sides were·

	RIGHT	LEFT
Upper forearm	4	4
Wrist	2 5	2
Hand	1 25	1 5

even less satisfactory. For example, the commonly used term elevation to indicate this position is inaccurate when the patient is supine. Extension, which was also considered, has the anatomic connotation of movement of the arms back from the dependent median plane position. A review of the literature and conferences with anatomists have failed to uncover a completely adequate term; hence hyperabduction is used with the foregoing qualifications.

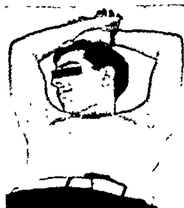


FIG 68.—Sleeping position, frequently seen in hospital wards, which in some individuals leads to obliteration of pulse and overstretching of nerve trunks

Usually the individual merely changes position during sleep or rests by bringing his arms down from his work and pays little attention to the discomfort. Few studies have mentioned the subject. Todd reported an experiment on himself in which he slept with his right arm stretched out almost parallel with his head. This was done with few interruptions from 1913 to 1921, when tingling, loss of sensation, swelling, desquamation, causalgia and paronychia developed in three months and affected especially the right thumb and finger. Todd reported that the experiment failed to disclose evidence relating to vascular changes, although the studies do not appear complete in that regard. The syndrome slowly disappeared when he ceased to sleep in this position. Thor-

the tips of the fingers from this syndrome Signs and symptoms in the 52 new cases carefully studied were:

1 Pain or aching (total 30)	
Hand	27
Arm	7
Shoulder	11
Shoulder hand	9
2. Numbness	26
3 Raynaud's syndrome (total 20)	
Female	14
Male	6
4 Paresthesias	18
5 Rubor cyanosis and/or swelling of hands	12
6 Weakness of arms and hands	8
7. Ulceration of finger tips	2

Many patients had two or more of these signs or symptoms.

The occupational importance of the syndrome has become increasingly impressive as we have studied more cases. Numerous workers in aircraft factories were forced to give up the riveting of the under surfaces of planes because they were unable to avoid the production of the syndrome after prolonged elevation of their hands in the position of hyperabduction. It also occurs in painters who paint ceilings or the under surfaces of ship decks and in garage mechanics who work in "pits" greasing and repairing the under surfaces of automobiles. Gangrene of the tips of the fingers occurred in a kiln worker who was obliged to keep his arms in the hyperabducted position a good portion of the time. Immediately on change of occupation, without known change of other factors, the gangrene healed. Examination disclosed that the pulses were completely obliterated in the position of hyperabduction

Several instances have been encountered in trapeze artists and we have reported the case of B. K who as a ballet teacher held her arms in hyperabduction an estimated three to four hours a day In this position her pulses are absent and oscillometric readings are zero bilaterally. Despite the fact that she has a left axillary venous thrombosis, recurrent Raynaud's syndrome, trophic changes in the tips of her fingers and reddened and swollen hands most of the time, we have been unable to persuade her to give up even the harmful phases of her career, to which she is devoted. The outlook appears progressively bad under these circumstances

Five patients have been seen with axillary venous thrombosis associated with the hyperabduction, and it has also been noted to

These were considered normal for the instrument used. Results of surface temperature studies performed under controlled conditions at room temperature (72 F) were all within normal limits.

Tests for obliteration of the pulses with the arms hanging between the knees when the patient was in the sitting position, with the arms flexed forward and with them abducted laterally parallel to the floor were all normal When, however, the arms were hyperabducted above the head, in several positions, the radial pulses were no longer palpable Oscillometric readings taken in these positions were zero for the right and left arms throughout their lengths This led to consideration of the possible relation of this phenomenon to the patient's condition Ordinarily the arms do not remain in hyperabduction long enough to produce serious ischemia even if the arterial lumens are obliterated

Questioning revealed that about two months prior to onset of the symptoms the patient had acquired the habit of sleeping with his arms hyperabducted The discomfort had never been sufficient to arouse him from sleep or to force him to bring his arms down He went to sleep at night and awoke in the morning with his arms in essentially the same position Examination while he was lying in his accustomed sleeping position demonstrated that the pulse was absent on palpation and by oscillometric study As far as it was possible to ascertain, his arms and hands were in a state of ischemia with relative nutritional deprivation for from seven to nine hours out of each 24 It was hypothesized that this might well be capable of causing symptoms and, in an extreme instance, initiate gangrene.

The best treatment appeared to be to force the patient to sleep with the arms caudal to the shoulder level This was achieved with some difficulty, necessitating the tying of his arms loosely to the posts of the foot of his bed so that they could not be abducted above the shoulder level. There was prompt response, the gangrenous areas healing within two weeks and the paresthesias disappearing in a month

John Beyer and I have published data on 52 patients who have had definite hyperabduction syndromes. Of major interest was the fact that 20 of them also had typical Raynaud's syndromes This was the first time such a relationship had been recognized. Numerous additional cases have been brought to my attention but not studied in detail.

Of all of these patients, six have had necrosis with gangrene of



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stro

[illegible] pulse is obliterated in position 2, a check is made to determine whether obliteration occurs in subject's usual sleeping position. This may be modified to include positions required in occupation, etc Use of an oscillometer with cuff applied at the wrist is a more objective method of measuring these changes

have complicated occlusive vascular disease such as arteriosclerosis and thromboangiitis obliterans

Stein studied the relation of position to blood pressure readings and demonstrated that in many persons as the arms become hyperabducted the blood pressure drops precipitously and in some is practically absent. This phenomenon may be responsible for misinterpretation in the operating room when, with the patient's arms in the position of abduction or hyperabduction, the anesthetist concludes that the patient's blood pressure is excessively low or that his pulse cannot be obtained.

It is also a problem to be considered in fracture or orthopedic work when the arm is put up in a cast or splint in the position of hyperabduction It is strongly recommended that the pulse be tested for in the fixed position and that serious attention be paid to any of the patient's complaints regarding paresthesias and active discomfort in hyperabduction.

Some patients present a mixed syndrome, with pinching by the scalenus anticus muscle and the neurovascular syndrome of hyperabduction Such a case was reported by Paull. Haggart has described three cases, and Evans has reported one associated with the carotid sinus syndrome.

To determine whether this syndrome was due to an abnormal arrangement of the anatomy of the shoulder girdle or whether it could be reproduced in a large percentage of normal individuals, Wright, Chinn and Millet studied 150 young adults considered to be without shoulder girdle or arm pathology. The following test was devised (Fig 69) which is practical for use by all physicians in the routine examination of their patients.

Wright test for hyperabduction syndrome—The subject is seated in a small straight-backed chair. The radial pulse is checked for its presence and strength in positions below the shoulder level Each arm is then hyperabducted with the examiner's fingers on the radial pulse. Subjects whose vessels are obstructed are easily checked by having them lie in bed and hyperabduct their arms.

corresponding arm The phenomenon is thus due to a normal, or at least a very common, anatomic arrangement but is produced relatively rarely as a symptom complex because few people maintain their arms sufficiently long in hyperabduction, especially after the position becomes uncomfortable. Neurologic symptoms including paresthesias were produced in only two subjects in the absence of alteration of the pulse

Eight subjects were able to block the pulse by muscular contraction when the arm was in a marginal position (the position in which a slight movement of the arm would obliterate or restore the pulse) In three the pulse could be obliterated in the marginal position by deep respiration In two others the pulse was definitely more prominent on deep respiration Thirteen of the 150 subjects frequently slept with their arms hyperabducted, usually with the elbows somewhat flexed Six of these slept comfortably in this position, and obliteration of their pulses was produced with difficulty and not in the position in which they usually slept. Seven frequently fell asleep with their arms hyperabducted but soon had sufficient discomfort to bring their arms below the shoulder level. In six of these, obliteration of the pulses was easily accomplished and occurred in the sleeping position which produced the symptom. One noted numbness in the right hand when tested by this procedure without obliteration of his pulse

The test disclosed a group of individuals in whom the pulse may be present intermittently In a position which first produces obstruction, the pulse suddenly becomes strong or disappears suddenly Change of position of the head sometimes affects the obliteration of the pulse Turning the head toward or away from the arm being tested may open or close the subclavian axillary artery

The degree of muscular development apparently has no effect on the incidence of arterial obstruction with hyperabduction Dr. Campbell Moses has written that he found no change in incidence in 28 wasted or chronically diseased patients One case has been seen in our clinic in a woman acrobat and contortionist It is, how-

Notations are made as to (1) whether the pulse can be obliterated in any position; (2) whether obliteration is difficult or easy to accomplish, in other words, whether there are many positions or only one specific position in which it can be achieved; (3) the position at which the pulse first disappears when the arm is hyperabducted, (4) whether deep inspiration produces obstruction of the artery when the arm is held in the marginal position (that in which a slight movement opens or shuts off the artery); (5) whether the incidence of this sign is influenced by muscular development, and (6) whether the neurologic symptoms can be produced within two minutes without interference with the major circulation as demonstrated by lack of change in the pulse

Extensive experience with this test has demonstrated that marked reductions in the pulse may be present, as proved by oscillometric readings, but cannot be accurately estimated by palpation For example, a decrease in oscillometric readings from 4 0 to 0 5 degrees may not be detectable by palpation yet cannot be held to be without significance It should be pointed out, however, that the oscillometric pressure at which the maximal swing of the needle occurs tends to decrease as the arm is elevated above the heart level. This is to be expected, but the pressure in the cuff must be adjusted to obtain the maximal reading at each position, e g , 45, 90, 135 and 180 degrees away from adduction

TABLE 8—OBLITERATION OF PULSE OF MAJOR ARTERIES OF THE ARMS OF 150 NORMAL INDIVIDUALS BY HYPERABDUCTION OF THE ARMS

DIFFICULTY	RIGHT OBLITERATED	LEFT OBLITERATED
I +	49 (32%)	48 (32%)
II ++	45 (30%)	47 (31%)
III +++	23 (15%)	22 (14%)
IV ++++	8 (5%)	7 (4%)
Total obliterated	125 (83%)	124 (82%)

On palpation (Table 8) the pulse was obliterated in 83 3 per cent of subjects on hyperabduction of the right arm and in 82 per cent on hyperabduction of the left arm. In some this could be accomplished only with considerable difficulty in manipulation, but in 62 and 63 per cent, respectively, obliteration of the right and left pulse was rather easily produced by hyperabduction of the



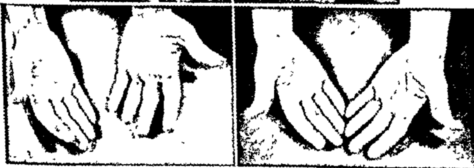


FIG 70 *(above left)* —Dissection of shoulder girdle Arm is in adduction Note adequate space for blood vessels and nerves without compression, stretching or torsion

FIG 71 *(above right)* —Arm in hyperabduction Note compression with actual pinching of subclavian vessels and brachial plexus between clavicle and first rib (Examiner's finger could not tolerate the pressure in that space) Note also stretching of axillary artery and nerves under the coracoid process and behind the pectoralis minor

FIG 72 *(below left)* —Hands of man, 47, in the habit of sleeping with arms in hyperabduction Numbness, paresthesias and pain developed in three months, but the relationship was not recognized Two months later discoloration of finger tips developed, as seen here Trophic changes were present in same finger tips

FIG 73 *(below right)* —Same patient one month after abandoning sleeping position of hyperabduction, with no other changes in régime Color is normal and all symptoms have disappeared (Figs 70–73 from Beyer, J A, and Wright, I S Circulation 4 171, August, 1951; reproduction from Medichrome Series MM—Vascular Diseases, by I S Wright and W. T Foley)

ever, generally difficult to obliterate the pulses in "loose-jointed" individuals

It should be emphasized that manipulation into the position of *hyperabduction is often erroneously used as a test for the scalenus anticus syndrome.* In this position the scalenus muscles are relaxed rather than tensed Frequently the pain or discomfort of the scalenus anticus syndrome is relieved by placing the hands in the position of hyperabduction In contrast, patients with the syndrome of hyperabduction are often relieved of the symptoms by placing their arms in the position of adduction, the position in which the patient with scalenus anticus syndrome is frequently most uncomfortable.

The pathologic changes must result from prolonged occlusion of the arterial supply and damage to the nerve trunks by stretching, pinching, prolonged ischemia or all three. Severe changes are relatively uncommon because (1) comparatively few people sleep or work (as in painting a ceiling) with their arms hyperabducted for long periods; (2) most of them will change position by bringing the arms below the shoulder level when discomfort develops, and (3) in many the arteries are obstructed or the nerves stretched excessively only in specific positions of limited range, so that, ordinarily, because of frequent changes in posture, the syndrome does not develop even from sleeping with the arms hyperabducted.

Dissections have revealed that there may be variations in the mechanisms responsible for this syndrome in different persons, and even in the same person with change of position of the arms Two points of torsion, stretching and pinching, operating either alone or jointly, appear to play the major role in most cases. One is the point at which the subclavian artery and vein, at the segment of the transition into the axillary artery and vein, and the main trunks of the brachial plexus pass posterior to the pectoralis minor, just beneath the coracoid process. They are all protected in adduction (Fig. 70), but when the arm is hyperabducted they are stretched around and underneath the coracoid process (Fig. 71).

By the same action the pectoralis minor is drawn tight. This double action results in varying degrees of stretching and pinching of the artery, vein and nerves in different persons.

The other point where pressure and torsion may be produced is [illegible] pass between the clavicle [illegible] more important point of [illegible]

[illegible] t rib was normal and the [illegible] echanism when the arm [illegible] severe symptoms, there [illegible] tenance of the position, [illegible] was admirably described [illegible] e to the costoclavicular [illegible] force his shoulders back-

tributed to the nutrition of the extremities in all of the cases reported

Table 9 presents points of differential diagnosis of the several significant syndromes of the shoulder girdle

TREATMENT

The treatment in most cases is simple and satisfactory, namely, avoidance of sleeping or working in the position of hyperabduction (Fig 73). If the patient is under surgical care, the physician must see that the arms are not maintained in hyperabduction in splints or casts unless it is so vital that the risk of development of this neurovascular syndrome is justified

Of particular interest is a group of patients in whom the hyperabduction syndrome has been associated with Raynaud's syndrome. In four, Raynaud's syndrome has been abolished by the simple expedient of abandoning the hyperabduction position.

Beyer and I reported the case of a 16 year old student with typical Raynaud's syndrome of the left second, third and fourth fingers on exposure to cold He had innumerable attacks during winter weather

Oscillometric readings became zero when the arms were elevated to 100 degrees Shortly before onset of Raynaud's phenomenon he had acquired the habit of sleeping with his arms in the position of hyperabduction In this position his pulses were found to be obliterated Since learning to sleep with his arms in positions more nearly approximating adduction he has gone through two winters without evidence of Raynaud's syndrome.

This experience strongly suggests that the irritation to the brachial plexus and perhaps also to the subclavian axillary artery in this syndrome is a competent producing cause of Raynaud's syndrome This would, of course, by no means apply in all cases of Raynaud's syndrome. It is not to be expected that this simple approach will "cure" a large percentage of such cases.

If the costoclavicular syndrome predominates, surgery may be necessary for relief, although this should be very rare. The logical procedure would be either to cut away a large portion of the anterior surface of the first rib or to remove the rib, as is done in

In addition to the difference in structural relationships, the wide range of reactions to the same positions depend in part on the great variation in rate of impairment of nerve conduction which follows compression of short segments of a peripheral nerve. In view of the studies of Denny-Brown and Brenner we have attributed this to uneven pressure gradients in the nerve bundles, with consequent variation in the degree of ischemia due to the escape of some small vessels It is thought that such a relationship is an expression of corresponding relative degrees of ischemia and not a direct consequence of pressure on nerve fibers.

The fact that tingling and numbness begin peripherally and progress centrally in our cases is in agreement with the principle of centripetal paralysis observed and formulated by Lewis, Pickering and Rothschild. They found that the sensations of cold and heat, and also muscular power, were subject to the same laws of centripetal paralysis after the production of ischemia by a blood pressure cuff The numbness which develops in the finger-tips is due not to a process in the finger-tips themselves but to changes in the portions of the nerves that lead to the finger-tips and which have been rendered ischemic. In their experiments, the amount of blood leakage was distinctly less than in our cases, in which only the subclavian axillary vessels are occluded and the many collateral vessels of the shoulder may function fairly freely. The nerves of the brachial plexus are nevertheless subject to ischemia. The ulnar trunk in the axillary area, since it is the lowest one, is most vulnerable to damage by stretching of this order, and this corresponds to the occurrence of paresthesias in the ulnar distribution in some of our cases.

The local gangrene of the tissues at the finger-tips in my first case was, I believe, the result of prolonged ischemia. It is thought that in all patients some blood must leak through the main vessels either continuously or intermittently, for otherwise massive thrombosis would probably occur. Collateral vessels must also have con-

Oscillometric readings	Confirmatory	Confirmatory	Normal	Confirmatory	Confirmatory
Surface temp. of fingers and hand	Cool in adduction	Same	Normal	Cool if prolonged in *aggravating* positions	Cool in hyperabduction
Evidence of venous obstruction	None	None	None	Pronounced dilatation of superficial arm and pectoral veins, especially in infra-red photographs	Pronounced only with primary axillary venous thrombosis
X ray	Cervical rib, unless only rudimentary fibrous bands exist	Neg	Narrow intervertebral spaces *late*, intraspinous air or radiopaque substances may demonstrate obstruction of canal	Angle shots may show asymmetrical thoracic inlet with narrowed space in aggravating postures	Neg
Venograms	Rare, or no abnormalities	Obstruction only if vein is pinched closed on adduction or turning of head	Normal	Blockage in some cases	Only if vein is pinched closed on hyperabduction with thrombosis
Local anesthetic	No value	If successful, temporary relief	No value	No value	Further studies needed
Treatment	Temporary relief in hyperabduction, surgery—excision	Relief on hyperabduction, surgery—severing scalenus anticus	Traction, immobilization, surgery—removal of disk, fixation	Mild cases exercises for improvement of postural tone of shoulder girdle muscles Severe cases removal of segment of offending rib	Relief in adduction, avoidance of hyperabduction

TABLE 9.—DIFFERENTIAL DIAGNOSIS OF NEUROVASCULAR SYNDROMES OF THE SHOULDER GIRDLE

	CERVICAL RIB	SCALENUS ANTICUS SYNDROME	RUPTURED NUCLEUS PULPOSUS OF CERVICAL SPINE	COSTOCLAVICULAR SYNDROME	HYPERABDUCTION SYNDROME
Age	Common in early-middle life or later	Same	Mostly in young adults, probably any age	Any	Only studies in young adults
Sex	Both	Both	Both	Both	Both
Symptoms	*Paresthesias, numbness*, pain in fingers and hand	*Same, tenderness* over scalenus area	*Intermittent*, paresthesias, numbness, anesthesias, pain in fingers and hand, pain and tenderness over disk	*Paresthesias, numbness*, pain in fingers and hand	*Same*
Signs	Cyanosis in adduction of hand, occasional *hyperhidrosis*	Same	Not striking	Cold, blue hands, tendency to chilblains — *Raynaud's* attacks	Normal color in adduction, pallor on hyperabduction in some
Gangrene	In extreme cases dry; highly painful	Same	Never occurs	Arterial thrombosis with gangrene in severe cases	In extreme cases, dry, highly painful
Aggravating position	Adduction with tension, as in lifting weight	Same, plus turning head from affected side	Extension of neck, straining, coughing	Back and down bracing of shoulders; hyperextension of neck	Hyperabduction of arms
Obliteration of pulse	Arms in extreme adduction or/and with head turning away from affected side	Same, true cases less common than formerly believed		60-70% of normals	Arms in various positions of hyperabduction; 85-90% of normals

Oscillometric readings	Confirmatory	Confirmatory	Normal	Confirmatory	Confirmatory
Surface temp. of fingers and hand	Cool in adduction	Same	Normal	Cool if prolonged in aggravating positions	Cool in hyperabduction
Evidence of venous obstruction	None	None	None	Pronounced dilatation of superficial arm and pectoral veins, especially in infra-red photographs	Pronounced only with primary axillary venous thrombosis
X-ray	Cervical rib, unless only rudimentary fibrous bands exist	Neg	Narrow intervertebral spaces *late;* intraspinous air or radiopaque substances *may* demonstrate obstruction of canal	Angle shots may show asymmetrical thoracic inlet with narrowed space in aggravating postures	Neg
Venograms	Rare, or no abnormalities	Obstruction only if vein is pinched closed on adduction or turning of head	Normal	Blockage in some cases	Only if vein is pinched closed on hyperabduction with thrombosis
Local anesthetic	No value	If successful, temporary relief	No value	No value	Further studies needed
Treatment	Temporary relief in hyperabduction, surgery—excision	Relief on hyperabduction; surgery—severing scalenus anticus	Traction, immobilization, surgery—removal of disk, fixation	Mild cases: exercises for improvement of postural tone of shoulder girdle muscles. Severe cases: removal of segment of offending rib	Relief in adduction, avoidance of hyperabduction

TABLE 9—DIFFERENTIAL DIAGNOSIS OF NEUROVASCULAR SYNDROMES OF THE SHOULDER GIRDLE

	Cervical Rib	Scalenus Anticus Syndrome	Ruptured Nucleus Pulposus of Cervical Spine	Costoclavicular Syndrome	Hyperabduction Syndrome
Age	Common in early-middle life or later	Same	Mostly in young adults, probably any age	Any	Only studies in young adults
Sex	Both	Both	Both	Both	Both
Symptoms	Paresthesias, numbness, pain in fingers and hand	Same, tenderness over scalenus area	Intermittent, paresthesias, numbness, anesthesias, pain in fingers and hand, pain and tenderness over disk	Paresthesias, numbness, pain in fingers and hand	Same
Signs	Cyanosis in adduction of hand, occasional hyperhidrosis	Same	Not striking	Cold, blue hands, tendency to chilblains — Raynaud's attacks	Normal color in adduction, pallor on hyperabduction in some
Gangrene	In extreme cases dry; highly painful	Same	Never occurs	Arterial thrombosis with gangrene in severe cases	In extreme cases, dry, highly painful
Aggravating position	Adduction with tension, as in lifting weight	Same, plus turning head from affected side	Extension of neck, straining, coughing	Back and down bracing of shoulders, hyperextension of neck	Hyperabduction of arms
Obliteration of pulse	Arms in extreme adduction or/and with head turning away from affected side	Same, true cases less common than formerly believed		60-70% of normals	Arms in various positions of hyperabduction, 85-90% of normals

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chest surgery Paull reported a case in which relief was obtained by developing the muscles of the shoulder girdle by suitable exercises and by stretching of the nerve trunks and blood vessels to reduce the amount of tension to which they were subjected. I had previously observed that it was difficult to produce this syndrome in loose-jointed individuals, and Paull used this as the logical basis for his technic.

The patient is suspended from a bar by his closely approximated hands while he relaxes the shoulder girdle muscles This is carried out three or four times each day, for as long a time as comfort permits. To build up the antagonists of the muscles which are stretched the patient should shrug his shoulders many times daily while standing erect and holding a 10–20 lb. weight in each hand.

If the patient's shoulders can be raised by strengthening the elevator muscles, the acuity of the angle of the neurovascular structures as they pass through the angle formed by the first rib and the scalenus anticus muscle should be reduced. This should reduce the irritation of the structures in this musculoskeletal angle. Elevation of the shoulder would also increase the costoclavicular space, thus lessening the hazard of pinching neurovascular structures at this point. Within two months Paull's patient reported marked improvement and three months later the improvement had been maintained This exercise technic deserves a fair trial in cases of this type.

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abscess in the artery wall. The commonest sites are the popliteal artery, the femoral artery at Scarpa's triangle, the axillary, brachial and intra-abdominal arteries. Essential polyangiitis often causes small aneurysms as a result of localized necrosis of the muscular coat of the arteries.

Congenital defects due to poor development of the musculature and some segments of arteries may produce aneurysms in any part of the arterial tree. One of the areas most frequently involved is the anterior portion of the circle of Willis and its branches. The rupture of aneurysms in this area is a frequent cause of death from cerebral hemorrhage. Multiple aneurysms which could not be explained on any other basis than that of congenital defect have been found in several cases.

Trauma is a common cause of both true and false aneurysms. This applies to the trauma of industrial accidents in peacetime as well as that of much greater incidence in combat during war. Large numbers of aneurysms, both with and without arteriovenous anastomoses, were seen in the vascular centers of the Army and Navy during the past war.

Pathology

Pathologically the following types of aneurysms are recognized. (1) Fusiform aneurysm, a rather uniform, spindle-shaped or fusiform dilatation of a segment of an artery. (2) Saccular aneurysm, which is a definite sacculation or outpouching from an artery, resulting from a sharply localized weakness usually in the medial coat (3) Dissecting aneurysm, which results from the splitting of the inner layers of an artery, after which the pressure splits the wall between the inner and the outer layer for varying distances. Sometimes communication is re-established at the far end from the original opening in the lumen. At other times a communication breaks through to surrounding tissue or a cavity, as the case may be (4) False aneurysm, which results from complete rupture

CHAPTER XI Aneurysms

AN ANEURYSM is an abnormal dilatation of a blood vessel resulting from a localized weakness and stretching of the wall of that vessel. Aneurysms are usually permanent. They have been recognized and described repeatedly since the time of Galen.

This chapter is devoted to arterial aneurysms. Most venous aneurysms are classified as varicosities and are discussed under that heading in Chapter XXIII Use of the term aneurysm to designate arteriovenous anastomosis or fistula is to be discouraged because aneurysm is not strictly a connection between an artery and a vein, although occasionally it occurs in combination with an arteriovenous anastomosis

ETIOLOGY

In the order of frequency of incidence, aneurysms may be due to (1) arteriosclerosis (by far the commonest type since syphilitic therapy has improved and average age of the population has increased); (2) syphilis and other infections (causing so-called mycotic aneurysms) that may weaken the vessel walls; (3) congenital weakness of the wall, (4) trauma, and (5) polyangiitis and other types of necrotizing arteritis.

. Infectious arteritis may be secondary to tuberculosis, actinomycosis, subacute bacterial endocarditis, septicemia, typhoid fever and other infections. Many arteries may be involved, the lesion frequently being in the vasa vasorum and associated with a local

of all coats of the artery and production of a sac, the wall of which is developed as a result of the laying down of successive layers of hardened blood clots A common site of false aneurysms is the popliteal space (Fig. 74).

In arteriosclerosis, the commonest cause of aneurysms, the pathology is usually localized destruction of the medial coats of the artery. The muscle fibers are replaced by fibrous tissue and are frequently ruptured and conspicuously malnourished from thickening and compression of the vasa vasorum. There is a tendency toward splitting of the inner layer, with the development of dissecting and later false aneurysms, although the first stage is usually fusiform or saccular Saccular aneurysms are most commonly seen in the popliteal arteries and the abdominal aorta, but may be found in any artery Fusiform aneurysms most often occur in the thoracic and abdominal aorta Dissecting aneurysms are generally confined to the aorta and may affect any portion of it Sometimes massive thrombosis is associated with arteriosclerotic plaques and dissecting aneurysms I have seen cases in which the entire lumen of the aorta was occluded by massive thromboses associated with a dissecting aneurysm, the aneurysm having taken over the function of the lumen of the aorta. Dissection at times extends into the branches of the aorta Arteriosclerotic aneurysms most often develop after the age of 55 They occur about 10 times as frequently in men as in women Complete rupture is much less common in arteriosclerotic than in syphilitic aneurysms

Syphilitic arteritis is a manifestation of tertiary syphilis The

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FIG 75 *(below)*.—Large, highly vascularized mixed tumor in popliteal space, previously diagnosed as popliteal aneurysm. This arteriogram clarified the diagnosis Compare with Figure 74



FIG 74 *(above)* —False aneurysm in popliteal space secondary to arteriosclerosis obliterans, caused by ½ in split through a calcified plaque in popliteal

The patient may be seized with an agonizing or tearing pain in the precordium, posterior surface of the thorax, lumbar region, abdomen or hip or thigh. Severe pain at the level of the first to the sixth thoracic vertebra should suggest the diagnosis. The patient is usually in shock. Syncope, convulsions, coma and paralysis of the lower extremities may all be present owing to involvement of various groups of blood vessels, depending on the level of the dissection. The arteries of the lower extremities may become pulseless as a result of organic obstruction or reflex spasm. The blood pressure often falls rapidly, and usually the blood pressure of the lower extremities is conspicuously lower than that of the upper extremities. Leukocytosis is common. Approximately one third of the patients die during the first few hours, and 50 per cent die within 24 hours. On the other hand, some patients have lived for many years. The course of patients who survive the first known attack is apt to be stormy. They are subject to repeated attacks as the dissection progresses and there is always a possibility of sudden death Rarely, even massive dissection is not accompanied by pain.

Nondissecting aneurysm.—Common sites of arteriosclerotic aneurysms are the popliteal, innominate, subclavian and common carotid arteries. As in the case of dissecting aneurysms in these areas and the aorta, the commonest site of origin is atheromatous plaques One aneurysm with its characteristic bounding pulsation should be an immediate challenge to search for others. I have found as many as seven aneurysms secondary to arteriosclerosis in a single patient, and the finding of a second popliteal aneurysm on the opposite side is common indeed. The second one is too often missed because of the clinician's preoccupation with the first aneurysm he encounters. The diagnosis can be substantiated by hearing a sharp systolic bruit with a single pitch on auscultation, by taking a flat x-ray plate for soft tissue studies to reveal calcification of the wall of the aneurysm and by making arteriographic

commonest site of involvement is the aorta, especially the ascending portion and the aortic arch Syphilis relatively seldom causes aneurysms of the abdominal aorta and peripheral arteries of the extremities.

A reasonable hypothesis seems to be that the fundamental lesion is secondary to direct involvement by spirochetes into the vasa vasorum and adventitia of the aorta. An inflammatory reaction is set up associated with lymphocytic infiltration and intimal proliferation of the vasa vasorum, which then becomes obstructed. This interferes with the nutrition of the medial coat of the aorta, causing weakness of the aortic musculature and a tendency for it to stretch at a particular point Interference with the normal absorption and transportation of cholesterol and other lipids may encourage the development of atherosclerotic deposits which in turn weaken the wall. Syphilitic aneurysms are fusiform or saccular. They enlarge slowly over a period of years or, occasionally, rapidly. They may assume large proportions and by erosion penetrate the thoracic cage Death occurs not infrequently as a result of rupture into the thoracic cavity or the pericardium, esophagus or vena cava Death from external bleeding following penetration of the chest wall is not uncommon The incidence of syphilitic aneurysms has decreased as a result of advances in antisyphilitic therapy After the diagnosis of syphilitic aortic aneurysm has been made, the average span of life is one to two years without treatment and five to 10 years with the best available treatment.

Signs and Symptoms

Dissecting aneurysm.—The onset of the symptom complex produced by a dissecting aneurysm of the thoracic aorta is often confused with that of acute, severe coronary thrombosis In several cases I have studied this has been further complicated by the presence of a reverse dissection which had proceeded toward the heart and interrupted the coronary circulation by involving one or more coronary arteries at their ostia.

liteal space, surgical obliteration or, less frequently, removal has been successful Transplantation of a portion of a vein to produce an end-to-end anastomosis of an artery which has been eroded by an aneurysm also has been tried frequently with varying success These are highly technical procedures and are not within the scope of this book They are discussed in detail in Pratt's monograph, *Surgical Management of Vascular Diseases*.

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studies The last are seldom necessary but may clarify the picture if surgery is contemplated.

Symptoms of nondissecting aneurysms of the thoracic aorta, regardless of etiology, vary greatly. Large ones may develop without symptoms, relatively small ones may develop rapidly and press against surrounding structures to cause pain very early. The pain is often substernal and transmitted to the back or to the shoulders, arms or neck It may be very severe and more prolonged than is common with the angina of effort. If the aneurysm is large enough, there may be symptoms of obstruction of the superior vena cava Dyspnea from tracheal or bronchial compression and a brassy cough with marked hoarseness may result from pressure on the recurrent pharyngeal nerve. Numbness of the arms is common A systolic murmur is frequently but not always heard over the aortic first or second area A diastolic murmur may develop later. In advanced cases the anterior wall of the aneurysm may be easily palpable as it becomes thinner Widening of the mediastinal area of dulness is sometimes but not always detected on percussion Frequently, x-ray study helps to clarify the picture by indicating the size and location of the aneurysm.

Treatment

There is no medical treatment for aneurysms except very small syphilitic ones, for which the cautious use of mercurials and bismuth is sometimes indicated. Arsenicals are apt to do great damage The value of penicillin in syphilitic arteritis is still not finally determined.

Surgical treatment has been developed for various types of aneurysms in different areas of the body. For large intrathoracic aneurysms of the aorta, electrolysis with a thin wire coil inserted within the aneurysm has been tried with varying results This procedure is not without danger, and at best the benefits are transitory. For many peripheral aneurysms, especially those in the pop-

an excessive demand was placed on the legs during active military training. So far as I know this type of production of the syndrome has not heretofore been described. It may occur in civilian life. Pratt has reported similar cases since the first edition of this book.

I have studied an unusual example of this type of problem in a nurse. She had never had any evidence of abnormality before working as an assistant to an oral surgeon, when she was obliged to stand with her arms extended in a strained position for hours each day. Her right arm began to enlarge and became painful. The diagnosis of axillary venous thrombosis was made, but the condition did not respond to therapy and the hand became progressively uncomfortable. Several physicians saw her, but none used a stethoscope on her arm or hand. This simple procedure, done on her first visit, established the diagnosis of widespread arteriovenous anastomoses. In a series of operations Dr. Pratt has severed and ligated hundreds of anastomoses but, as is typical of this condition, new ones tend to open up. The situation seems under control, with one residual murmur above the elbow, but one cannot be too sanguine regarding the future.

Dr. Lawrence W. Smith has encountered a similar case in which the rather inactive congenital anastomoses were aggravated by work as a riveter in an aircraft factory. Eventually gangrene of the hand developed and amputation at the elbow was necessary.

Traumatic arteriovenous anastomoses are mistakenly believed to be confined to injuries produced by penetrating wounds. A severe bruising blow which traumatizes the walls of the two vessels can result in arteriovenous anastomosis.

I saw such an instance in a young girl who fell from a back porch onto a pile of rough gravel. The left [illegible]
after the fall, and an arteriovenous [illegible]
proved surgically. A similar case [illegible]

The traumatic type is especially common during war, when all manner of shrapnel and bullet wounds are responsible. In peacetime the possibilities are almost unlimited.

For example [illegible]

CHAPTER XII Arteriovenous Anastomoses

By arteriovenous fistula or anastomosis is meant any abnormal vascular channel directly connecting the arterial with the venous side of the circulatory tree. The connecting channels may be either congenital or acquired. The condition was first recognized by William Hunter, who described it in 1757. It has been known since then by a host of names, few of which are accurately descriptive.

Etiology

Congenital arteriovenous anastomoses arise from failure of the common embryologic analogue to differentiate into artery and vein. In view of the common bed of the vascular tree it is understandable how multiple lesions may, and frequently do, occur. During the past war I encountered for the first time a group of patients in whom congenital arteriovenous anastomoses produced symptoms rather suddenly. These were men who had led sedentary lives prior to entrance in the Army. After a few months of heavy exercise with much running and climbing, to which they had never before been exposed, what appeared to be large varicose veins developed in the lower extremities. Several of these men were scheduled to undergo ligation procedures on that basis. Careful study, however, demonstrated that the lesions fulfilled the criteria for true congenital arteriovenous anastomoses. The explanation appeared to be that the channels of arteriovenous anastomoses had always been present but had been latent and never opened until

enable us to present the picture of acquired arteriovenous anastomoses.

The establishment of a communication leads to the following immediate results (1) A fall in the general arterial blood pressure affecting both the systolic and the diastolic level. (2) An increase in pulse rate. (3) An increase in venous pressure, proximal as well as distal to the fistula, with the increase slight or pronounced according to the size of the fistula. (4) An increase in cardiac output, depending on the size and location of the fistula. (5) A very temporary decrease in the size of the heart and of the artery proximal to the fistula owing to the sudden diversion of blood from the arterial to the capacious venous system—an alteration comparable to that seen in massive hemorrhage

The establishment of a fistula also has more remote effects (1) A permanent diversion of the circulating blood from the normal capillary bed into the fistulous circuit (2) A gradually increasing total blood volume, proceeding pari passu with the amount of blood diverted through the fistula. (3) Gradual dilatation of the heart and of the artery and vein proximal to the fistula, due to the distending effect of an increased volume or bulk of blood attracted to the fistulous circuit because of its diminished resistance (4) The development of an extensive collateral circulation due to lowered resistance to the flow of blood at the site of the fistula In the presence of a constriction of the artery proximal to a fistula (a rare occurrence clinically), this extensive collateral circulation pools blood into the artery distal to the fistula, thus causing dilatation of the artery distal to the fistula instead of proximal to it (5) Slight hypertrophy of the heart due partly to dilatation and overdistention and partly to the increased work required to propel the increasing volume of blood flowing through it The cardiac enlargement is due mainly to dilatation and only to a minor degree to hypertrophy (6) Gradual recovery from the lowered blood pressure noted immediately after formation of the fistula, the systolic being equal or higher and the diastolic definitely lower than before formation of the fistula, thus greatly increasing pulse pressure

The volume of blood diverted through the fistulous circuit depends on the size of the fistula, its location in the arterial tree and the absence of any obstruction in the veins proximal to the fistula A small communication causes only slight changes that may not be detected. With the precision instruments now available, the slight alterations necessary to compensate for a small leak are not demonstrable, nor do these altera-

story window and in the fraction of a second that the patient's leg was back of her during running, the blade penetrated the popliteal space The wound quickly healed, but resulted in an arteriovenous anastomosis (For further details, see Chapter XXIX)

A tinsmith aged 46 was cutting Allegheny metal when a portion of it sprang back and cut him severely across the posterior surface of the wrist, severing tendons and blood vessels. The tendons were successfully sutured, but several arteriovenous anastomoses remained This case is described in detail in Chapter XXIX.

The history given by a patient will, in most instances, immediately differentiate between the congenital and the acquired type. Usually in the congenital type the signs and symptoms have gradually developed in the course of the patient's life span. In the acquired type symptoms and signs have developed relatively rapidly, usually following an injury such as a gun shot, stab wound or severe bruise It is often forgotten that arteriovenous anastomoses can occur as a result of surgery.

Pathology

Each anastomosis, whether congenital or traumatic, may have one or more of the following characteristics. It may represent simply a direct communication between an artery and a vein. It may be an aneurysmal sac between the artery and the vein. It may be an aneurysmal sac on the arterial side with a communication to the vein. The artery and vein may have a common opening into an aneurysmal sac In the congenital type there may be large, ill-defined pools or sacs which have multiple openings from surrounding arteries into venous sinuses or tracts that eventually empty into definite veins Arteriovenous fistulas, both congenital and acquired, may occur at any point in the body.

Emile Holman has admirably summarized the results of the experimental establishment of arteriovenous anastomoses and of closure of such communications. Free citation from his work* will

* Reprinted here by permission of the author. From Holman, E: *Arteriovenous Aneurysm: Abnormal Communications between the Arterial and Venous Circulations* (New York: The Macmillan Company, 1937).

correlation between an experimental study and what actually occurs in a pathologic clinical condition.

In man arteriovenous anastomoses have a number of forms A congenital arteriovenous anastomosis may be single, but most cases I have observed have shown multiple lesions and in some instances literally hundreds of small arteriovenous anastomoses located, for example, from one end of an arm to the other (Fig.

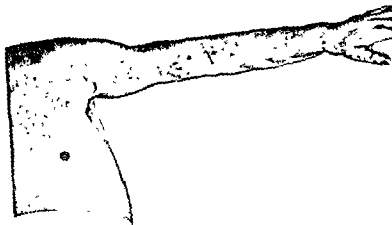


FIG 76—Innumerable congenital arteriovenous anastomoses of left arm of a young man Such extensive involvement may lead to cardiac dilatation and failure Surgery offers the only hope of relief, but is difficult and often unsuccessful Ultimately disarticulation at the shoulder may be necessary

76) Such extensive involvement presents a serious, if not insoluble, therapeutic problem As numerous fistulas or anastomoses are closed surgically, others appear within three to 12 months. The new ones apparently form from latent channels that do not begin to function until the original channels are closed off, thus changing the pressure within the arterial tree In some instances multiple operations have failed to control the problem and major surgery such as disarticulation of the arm at the shoulder has been necessary Fortunately these are the exceptions rather than the rule

tions produce visible visceral changes. A larger fistula may result in changes, only some of which are demonstrable A fistula larger than the feeding artery, or large enough to divert a considerable amount of blood back to the heart, invariably produces remarkable changes, both immediate and remote. That the same changes to a greater or lesser degree occur in the presence of every fistula, no matter what the size, seems unquestionable. The extent of change in each case depends entirely on the volume of blood diverted through the fistula.

Certain immediate changes are noted on closure of the fistula by compression or incision. (1) A rise in the general arterial blood pressure to a high point for several beats, followed by a fall to a lower level, but above that which was present before production of the fistula This rise involves both diastolic and systolic levels The rise in diastolic pressure depends primarily on the elimination of the area of lessened resistance at the site of the fistula. The rise in systolic pressure depends not only on an increased peripheral resistance but also on distention of the arterial circulatory bed by the volume of blood which had escaped into the veins through the fistulous tract. (2) Marked, immediate retardation of pulse rate and subsidence of the vigorous cardiac activity. (3) A decrease in venous pressure proximal to the fistula (4) Marked decrease in cardiac output. (5) A temporary increase in size of the heart due to overdistention of the central circulatory bed by the volume of blood formerly coursing through the fistulous circuit into the capacious venous system. These immediate changes are produced not only by direct closure of the artery feeding the fistula but, to a lesser degree, by closure of the vein leading from the fistula toward the heart.

Four remote effects follow repair or excision of the fistula (1) A gradual readjustment of the general blood pressure, the systolic falling to about the level present before elimination of the fistula and the diastolic remaining higher than with the fistula open The result is a decreased pulse pressure as compared to that present with the fistula open. (2) Gradual decrease in total blood volume, which is the real cause of the fall and readjustment of blood pressure in the first few days after repair of the fistula. (3) Gradual recovery to a normal pulse rate. (4) Gradual subsidence of dilatation of the heart and of the proximal artery and vein, proceeding pari passu with the decreasing bulk of blood flowing through them.

The foregoing description by Holman represents an excellent

correlation between an experimental study and what actually occurs in a pathologic clinical condition.

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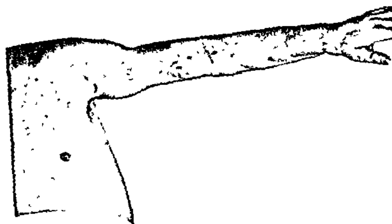


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Signs and Symptoms

Both congenital and acquired types have been observed intracranially, in the region of the head, mouth and jaw (Figs. 77 and 78), the neck, supraclavicular area, thorax, abdomen, back, buttocks, arms, legs, hands, fingers and toes.

When an extremity is involved the affected limb becomes swollen, engorged and in long-standing cases actually elongated. In young people, the bones increase in length due to the increased blood flow to the epiphyseal line during the period of growth. This may be accompanied by a feeling of stiffness or even pain. The veins of the affected extremity become markedly engorged because of the arterial pressure shunted directly into them. The blood pressure of the extremity is higher than that of its mate, especially if the anastomosis is large enough to produce a bruit. The patient often complains of murmur or bruit which radiates from the extremity; in the case of arteriovenous anastomosis of the thorax and head, it may be loud enough to cause the patient great discomfort. With congenital arteriovenous anastomoses, there are frequently an increased growth of hair and increased sweating in the affected regions. The involved area shows a definite increase in temperature over that of the opposite side. In the lower extremity, ulcers appear in the region of the ankle or foot in about 50 per cent of the cases.

Cardiac dilatation and hypertrophy are common complications of arteriovenous anastomoses, being more usual in the acquired than in the congenital type. The bradycardia produced by pressure on the artery proximal to large anastomoses was first noted by Nicoladoni in 1875 but named for Branham, who noted it again in 1890. The oxygen content of venous blood drawn from the superficial or, in indicated cases, from the deep veins of the involved extremity is far higher than that of the normal extremity. This is often demonstrable simply by using two test tubes to show the lighter (arterial) color of the blood of the affected side.

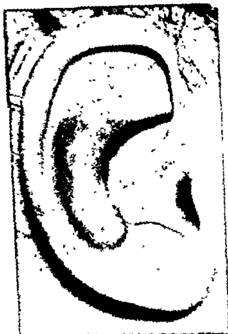




Fig 77 *(above)* —Congenital arteriovenous anastomosis of vessels of external ear

Fig 78 *(below)* —Congenital arteriovenous anastomosis of vessels of upper lip (This and Figure 77 reproduced by courtesy of Dr Gerald H Pratt)

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of several hours a day to obliterate the small lesions may encourage thrombosis The results of the procedure are not predictable.

For large single anastomoses, and even when there are several well defined anastomoses, surgical closure is the procedure of choice for several reasons. (1) Prevention of cardiac enlargement

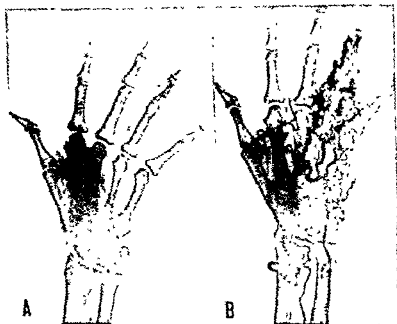


FIG 79—Multiple congenital arteriovenous anastomoses *A*, conventional x-ray, showing enlargement of right fourth finger *B*, arteriogram, showing conspicuous convolutions of involved vessels

with development of insufficiency. In the presence of cardiac enlargement proved by serial x-rays, it is imperative that an attempt be made to ligate the anastomosis before cardiac failure occurs (2) Prevention of the development of venous insufficiency with varicose veins or evidence of venous stasis. (3) Prevention of enlargement of the limb, both in circumference and in actual length if the epiphyses have not closed. In cases of traumatic arte-

Blood for the chemical determination of oxygen unsaturation should be carefully drawn under oil to avoid changes due to exposure to air before analysis

Arteriography with an opaque substance such as Thorotrast is useful for diagnosis and often an important aid in analyzing the situation before surgery is attempted. By means of arteriography, often the size and site of the fistula, the mechanism of the circulation in the limb below the fistula and the presence of multiple fistulas can be established.

Treatment

It should be remembered that occasionally arteriovenous anastomoses, both congenital and acquired, close spontaneously, although this cannot be anticipated in any specific case. I have seen two examples of spontaneous closure of congenital arteriovenous anastomoses in the vessels of the scalp.

In one, for example, persistent bruit had been present for 2½ years, was loudest over the occipital region and could easily be heard on stethoscopic auscultation A definite, prominent pulsation was palpable in this area The bruit was a source of great annoyance to the patient, especially when he tried to sleep, at which time the constant pulsating and buzzing in his head interfered with proper rest Surgery was contemplated Suddenly and without explanation the signs and symptoms completely cleared This was in 1941. Since then the patient has spent nearly four years in the Army and in 1951 had had no recurrence.

I have seen several examples of small arteriovenous anastomoses due to war trauma which were spontaneously obliterated with total disappearance of all symptoms. Such instances are rare, but if the anastomoses appear to be very small and there is no evidence of cardiac strain, conservatism for a period of time is sometimes more worth while than surgical exploration for an anastomosis which may be so small that it will be difficult to locate or which may prove to be multiple, very small anastomoses.

Continuous pressure by means of a pressure sponge for periods

portion of the neck and the left side of the jaw. A loud bruit could be heard throughout the cardiac cycle, the mass was steadily enlarging and there was no choice but surgery Incision revealed an enormous

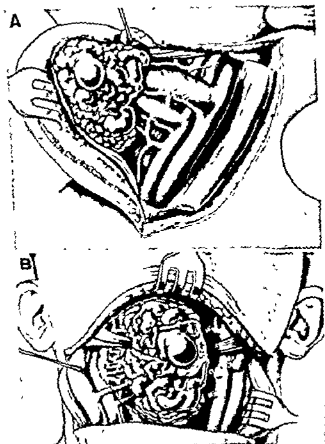


FIG 80—Congenital arteriovenous anastomoses in neck of young woman, with innumerable connections with all major vessels of neck. *A*, lateral view, *B*, anterior view (Courtesy of Dr Gerald H Pratt)

vermiform mass of blood vessels with almost innumerable connections with the jugular veins, carotid and thyroid arteries and many other vessels (Fig 80) Pratt ligated the vessels and removed the mass, but

riovenous anastomoses it is suggested that adequate time be allowed between the trauma and the surgical procedure to permit the establishment of satisfactory collateral circulation. The optimal time appears to be three to six months. In the hands of skilful surgeons the results of surgery for single traumatic arteriovenous anastomoses are good.

The results of surgery for congenital arteriovenous anastomoses are often discouraging, principally because of the multiple communications, many of which are latent and unused and hence are not detectable at the time of the first or second operation. During the first five years of observation it is not uncommon for three to five operations to be necessary to occlude effectively all of the anastomoses in, for example, a finger. When an entire extremity is involved the situation becomes almost impossible, and in more than one instance it has finally become necessary to disarticulate a limb. However, the progress of the condition can be retarded somewhat and pressure can be taken off the heart by repeated operations to minimize the number of open channels.

A patient, first seen at age 13, had a history of slowly progressive enlargement of the right fourth finger since the age of 2. Figure 79, *A*, is a conventional roentgenogram showing enlargement of the finger, and Figure 79, *B*, an arteriogram showing conspicuous convolutions of vessels involved in multiple arteriovenous anastomoses. Numerous bruits could be heard throughout the finger and hand. Three operations have been performed by Dr Gerald Pratt. No bruits can be heard in the hand, one bruit of moderate intensity is audible above the wrist. The hand, although somewhat swollen, functions well. There has been no change for six years and no cardiac changes are demonstrable. Exercise capacity is excellent. A conservative course with periodic observations will be followed.

Sometimes repeated surgery is the only alternative no matter how serious the situation.

A young woman has been observed with Gerald Pratt for more than 10 years. When first seen a large pulsating mass involved the upper

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[illegible]

we predicted that there would be a recurrence Since then, at intervals of two or three years, further surgery has been required. Frequently, no bruit could be heard for six to 12 months after operation, but sooner or later a bruit appeared

By means of careful plastic surgery, marked disfigurement has been avoided The patient has maintained a normal existence which most certainly could not have been possible had not repeated surgical procedures been undertaken. The last operation was done in March, 1946, at which time a very small bruit was found to be due to a single arteriovenous anastomosis This was ligated, with complete cessation of the bruit. In 1950 marked enlargement of the left side of the tongue was noted, but no bruit could be heard. The prognosis for this patient regarding freedom from further surgery is definitely guarded. Her life does not seem to be in jeopardy and she is leading a normal existence

Careful work by Pratt and others has demonstrated that even the necessity for repeated operations is not per se sufficient argument for early amputation The decision to amputate should be made only when the number of anastomoses is overwhelming and when, despite repeated surgery, the limb is becoming unmanageable or the cardiac status is deteriorating rapidly.

The choice of surgical procedure depends on the individual circumstances and need not be discussed in detail here. If there is a simple anastomosis between one vein and one artery it is generally best to ligate the vein and the artery above and below the site of the anastomosis and to remove the H segment, including a portion of both artery and vein and the intervening anastomosis Unfortunately the findings on exploration are frequently too complex to permit this easy procedure, and the surgeon must devise the best approach to the problem as he finds it.

The use of supportive rubber bandages, elastic stockings or arm supports may reduce the tendency to development of large venous channels with congenital arteriovenous anastomoses of the extremities. The pressure confines the blood to the deeper and frequently the normal channels.

followed by sudden exposure to cold Sensitivity to cold can sometimes be transferred by the intradermal injection of blood serum from a reactor to cold, but students of allergy hesitate to classify this as a true allergic phenomenon.

Diagnosis.—The history will usually indicate the correct diagnosis It can be confirmed by several simple measures. If the patient is sensitive to cold, placing an arm in a container of water at 12–14 C (53–57 F) will cause an urticarial type of reaction in the portion exposed to the cold water in five minutes Frequently a systemic reaction, with reduction of blood pressure and increase in pulse rate, develops Syncope may occur in persons with extreme hypersensitivity. The application of an ice cube to the forearm for four or five minutes also serves as an adequate test. Characteristically a marked urticarial wheal appears and frequently urticaria is noted to follow the course of the cold water which flows over the arm from the melting ice cube Figure 81 shows a simple demonstration of cold sensitivity of the urticarial type. A cube of ice placed on the right forearm for three minutes induced a wheal (arrow) Simultaneously the left hand was placed in water at 4 C This caused swelling and tenseness of the skin of the entire hand, and a generalized histamine-like reaction occurred, with a drop of 30 points in systolic blood pressure, throbbing in the head and striking flushing of the face

The following detailed study of cold sensitivity was made in one of our cases.*

Experiment I—The temperature at which a reaction would take place was determined by applying a small flask filled with water to the forearm for a few minutes The temperature of the water was gradually reduced, the temperature at which the reaction occurred is shown in Table A. Because the results seemed improbable, since the temperature causing the reaction was unbelievably high, the test was repeated and verified One would expect that this patient would be in a constant

* Reported in Saylor, L. L., and Wright, I S . Studies on two cases of urticaria from cold sensitivity and of the effect of histamine treatment, Am J M Sc 192 388-395, September, 1936

CHAPTER XIII: Syndromes Produced by Temperature Changes (Excluding Raynaud's Syndrome)

HYPERSENSITIVITY TO COLD WITH URTICARIA AND OTHER HISTAMINE-LIKE RESPONSES

MANY CASES of hypersensitivity to cold have been reported since Béhier described his own case of cold urticaria in 1886. Duke, Horton and Brown, and Lewis made careful investigations of this interesting phenomenon. A survey of their work demonstrates that hypersensitivity to cold can be made manifest by a variety of means: (1) by allergy; (2) by autoantigens; (3) by histamine-like substances; (4) by underlying vasomotor disturbances; (5) by disturbances of the central temperature-regulating mechanism.

Characteristically, an urticarial reaction develops on a portion of the body exposed to cold. There is frequently a measurable or perceptible systemic reaction, indicated by a drop in blood pressure, an increase in pulse rate and the appearance of a flush over the face and neck. If the exposure, and hence the skin reaction, is widespread the systemic reaction may be sufficient to produce collapse. Horton made the important observation that unexplained drownings may occur in patients hypersensitive to cold who plunge into cold water and suffer a systemic shocklike reaction. In some individuals the reaction is more apparent after exposure to heat

state of edema as soon as the room temperature reached 24 C. (75.4 F.), but this was not the case A modification of the test showed that the reaction depended entirely on actual temperature of the skin, which represented a resultant of the temperature of the object in contact with it, the heat conductivity of the object and the generation of heat

TABLE A.—Temperature at Which Reaction Occurred *

Room Temp C	Temp of Material Applied, C.	Time of Contact, Min	Reaction
25	26 4	4	Neg
25	25 4	4	Neg
25	24 0	4	Redness, distinct wheals

* Control skin temperature at room temperature was 31 4 C

by the tissues beneath the point of contact This was demonstrated by the following observations The patient, while seated in a room of 22 3 C temperature for over an hour, had no reaction Skin temperature of the arm was 31 4 C A metal cabinet, a permanent fixture in the room, had a temperature of 23 5 C, or 1 2 degree higher than the room temperature The cabinet, however, seemed cold, since it removed heat from the arm in contact with it more rapidly than did the air, consequently the arm became cooler after contact with the metal for four minutes, and skin temperature at the point of contact was reduced to 27 C Definite redness and edema appeared at the point of contact

Experiment 2.—The blood pressure, pulse and skin temperature and changes in size following the production of edema in one hand and wrist were recorded (Table B)

TABLE B.—Response to Reaction with Hand and Wrist in 8 C Water for 5 Minutes

				Temperatures C			
Time	B P	Pulse	Wrist Circum	Room	Back of Hand	Right Cheek	Left Cheek
Control	140/86	102	15 75	24 6	32 5	35 8	35 1
10 min after removal	124/70	124	18 0	25 5	34 6	35 8	35 8

Experiment 3.—The patient's generalized response to induced cold urticaria was similar to that on subcutaneous injection of 1 cc of 1 1,000 histamine hydrochloride (Table C)

TABLE C.—Comparative Response to Histamine Injection

Time	B P.	Pulse	Cheek Temp., C
Control	146/90	92	34 2
After histamine			
5 min	132/68	135	
10 min	130/60	140	
15 min	126/76	126	36 3

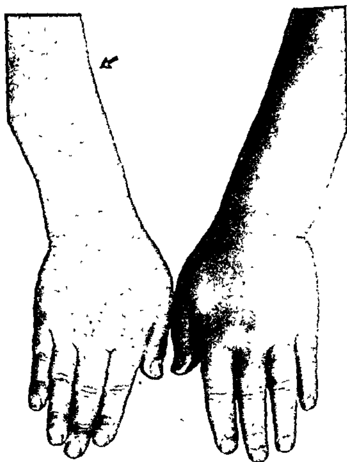


FIG. 81.—Reaction to test showing sensitivity of urticarial type Left hand was immersed in ice water at 4 C. for two minutes. It is swollen and tense, with many wrinkles less pronounced than in the right hand An ice cube applied to right forearm produced an urticarial wheal (arrow).

Experiment 9.—The Prausnitz-Küstner reaction was observed. Venous blood was taken before and 25 minutes after exposure of the hand to ice water for five minutes, the second specimen being taken 18 minutes after edema had appeared and when it seemed to have reached its maximum. The serums were separated and injected intradermally in a normal person and the area cooled for five minutes with ice. No wheal was formed, although Levine had found six positive and five negative reactions reported in the literature.

Experiment 10.—By transferring edema fluid from an area free from edema before application of ice to the area, Levine had produced a secondary urticarial wheal. Normal saline was used both as a vehicle to infiltrate the edema and recover the edema-producing substance and also as a control injection In this patient, similar results were obtained: within three minutes of injection of 0.2 cc of edema fluid, an area of urticaria 2 $\times$ 2 cm. appeared, and with 0.2 cc. of normal saline no urticaria appeared

A characteristic case seen in our clinic was that of a young woman who noted that when she carried milk bottles which had been on ice the inner surface of her arm against which the milk bottles rested became hot, swollen and itchy and that her face flushed and felt very warm. Immersion of her hand in cold water produced a typical histamine-like generalized response as well as the local response of which she complained Another young woman had a severe choking spell after eating ice cream. This occurred several times before its significance was appreciated A third patient, a man aged 44, developed urticaria over most of his body after taking a cold shower, associated with palpitation and weakness He too was demonstrated to be sensitive to cold.

It might be added at this point that it is possible that individuals have died of so-called heart disease from exposure to extremely cold showers The cause of death in some may well have been syncope secondary to hypersensitivity to cold A case has been reported from Mayo Clinic of extreme hypersensitivity to cold even on a change of temperature of the air The patient nearly drowned on several occasions while swimming Observation established beyond doubt that he was extremely sensitive to cold and collapsed on

Experiment 4.—Exposure of a localized area of skin to cold caused definite local vasodilatation, prominent redness of the skin and marked decrease in skin temperature of the exposed area (Table D). The blood

TABLE D.—TEMPERATURE (C) RESPONSE AFTER HAND AND WRIST WERE IN 8 C WATER FOR 5 MINUTES

Time	Room	Back of Hand	Mid-Arm	3d Finger	Left Cheek
Control	24.6	31.3	31.6	32.2	34.3
10 min after exposure	24.6	35.7	34.1	33.6	36.1

pressure readings during the experiment were: control, 142/90, after hand was in water two minutes, 146/94; after three minutes, 130/88, after five minutes, 122/84, and after the hand had been removed for 10 minutes, 138/94. Pulse rate on beginning the experiment was 106 and after the hand had been in the water for five minutes, 112.

Experiment 5.—Although Bray and Levine both demonstrated local eosinophilia in wheals produced by exposure of the skin to cold, two tests in this case gave negative results.

Experiment 6.—Horton and Brown demonstrated the histamine-like effect of the production of cold urticaria on gastric acidity. The results in this case confirmed their findings (Table E). The hand was placed

TABLE E.—HISTAMINE-LIKE EFFECT OF COLD URTICARIA ON GASTRIC ACIDITY

Specimen	Free Acid	Total Acid
Fasting	43	59
10 min. after hand was removed	78	90
20 min. after hand was removed	92	106

in water at 10 C for 10 minutes. A tourniquet at the elbow was removed in five minutes. The patient noted a general effect, with throbbing in the head, 2½ minutes after the hand was removed from the water.

Experiment 7.—In the Perutz, Brugel, Greenfield test, in which 10 per cent menthol in alcohol is applied to a skin area, the positive reaction takes two forms: the reaction is the same as that induced by cold, or the area becomes more sensitive to cold. The response in this patient was negative. An area of redness resulted, but there was no urticaria or increased sensitivity to cold.

Experiment 8.—An area 5 × 8 cm. in the deltoid region was anesthetized with 2 per cent novocain injections until all sensation to cold was lost. A test tube containing ice was then applied for five minutes. Edema appeared in the anesthetized area, but was not as marked as that in unanesthetized skin.

Histamine hydrochloride 1:1,000 solution is used. The first injection is 0.1 cc. subcutaneously. Twice a week the patient receives intracutaneous injections, with each dose increased by 0.1 cc. until 0.5 cc. is reached. The injections are then continued subcutaneously, each dose increasing by 0.1 cc. until 1 cc. is reached, following which the dosage is continued at 1 cc. twice a week.

Patients frequently experience relatively severe reactions before the high dosage is reached. In these circumstances it is necessary to continue with the dose currently being administered or, if warranted, to decrease the dose to such a point that a reaction is produced, but one of minimal order. In some patients the 1 cc. dose can never be administered. Nevertheless desensitization may take place at a lower dosage.

Results of this type of treatment are frequently not too spectacular. A number of patients have improved to the point where exposure to cold weather does not cause undue disfigurement from urticarial wheals. In others improvement has developed to a point where systemic shock is not an important consideration. Most of our patients have, however, continued to have local or generalized reactions of some degree on exposure to cold or heat.

Drugs that act as histamine neutralizers exert a favorable effect in some cases. Benadryl has been administered in doses of 50–100 mg. three times a day prophylactically or on the development of cold urticaria. Pyribenzamine hydrochloride has proved helpful in some, but not all, cases. Untoward reactions to these drugs may include nausea, drowsiness, dryness of the mouth, weakness, dizziness and headache.

Frostbite

Perhaps the most important syndrome which results from exposure to cold is frostbite.

Etiology.—In peacetime it is encountered especially in individuals who work outdoors in very cold climates, although the increasing popularity of winter sports has added to the incidence of frostbite.

In wartime, if campaigns are conducted in cold climates or even

any exposure to cold. I have had a patient with similar sensitivity.

An actress was accustomed to swimming in the cold water off the English coast. One day while swimming she collapsed and was pulled from the water. At this time she suffered from nausea, severe vomiting and hives, first attributed to indigestion from eating of a lobster salad The following day she dove into the cold water and again had to be rescued; the same symptoms were present. For three years thereafter she had to forego swimming The correct diagnosis was not made, however. She then had a period of four years without evidence of the syndrome. While playing in an operetta in New York during a cold winter, the syndrome returned. This time exposure to cold air caused enormous urticarial welts, and it became necessary for her to reach the theater two or three hours before performances in order for the reaction to subside sufficiently for her to make a stage appearance.

This syndrome is of great interest and is frequently missed It is undoubtedly much more common than is generally recognized and every physician should be on the lookout for it.

In contrast to this condition, some individuals have marked sensitivity to heat. Urticarial reactions follow exposure to hot environmental temperatures, the development of fever or exercise that causes an increase in body temperature Such persons seldom have as severe reactions as those with hypersensitivity to cold. I know of no proved instance of true hypersensitivity to both heat and cold in the same individual.

Treatment.—This is not completely satisfactory. Ideally, treatment should be directed toward desensitizing the patient. This can be approached theoretically by several methods. One is to expose the cold-sensitive patient to progressively cooler baths by reducing the temperature of the bath 1 degree (C.) each day or to expose the hand to progressively lower temperatures, the idea being to have the patient release his own histamine-like substance in gradually greater quantities and thus to desensitize himself Another method of desensitization is to administer histamine, as originally suggested by Horton. The method of histamine desensitization which we have used follows.

of the heating equipment failed and frostbite followed. As time went on, the incidence of frostbite in high altitude bombing was markedly reduced, except when flak or bullets from enemy planes produced vents in the plane's structure.

Pathology.—Exposure to severe cold causes vasoconstriction both locally and as a result of general reactions This continues for some time. The resulting anoxemia seriously affects the local tissues. In addition, frozen crystals of tissue fluids form, and when these thaw out the cells are ruptured and membranes break down to produce necrosis Thrombosis of the smaller arteries occurs, increasing the tendency to death of the tissue and gangrene.

Lewis demonstrated that the true freezing point of skin is between —2 and 0 C (28 4 and 32 F.) Freezing does not normally occur at this level because of the law of supercooling. By supercooling is meant the ability of a substance to undergo cooling below its ordinary freezing point without actually solidifying. Numerous factors enter into the production of and interference with supercooling in man, among them dryness of the skin, production of oil and recent washing. Freezing of the skin frequently occurs between —4 and —10 C. (24 8 and 14 F), but occasionally it does not occur until a level of —15 to —20 C. (5 to —4 F) is reached. Factors which encourage freezing are (1) increased dampness of the air, (2) exposure to wind, which increases the evaporation of sweat and removes the layer of radiant heat from around the body; (3) circulatory stasis and anoxemia The last is especially important in combat because it is frequently dangerous for the patient to move about to reduce the tendency to stasis. The wearing of tight boots was found by the Germans to be disastrous during the Moscow campaign, the loose boot or mukluk being much more satisfactory.

An important element in the production of frostbite in civilian life is peripheral vascular disease I have seen numerous individuals who were brought to their physicians because of frostbite and

in so-called warm climates in which sudden drops in temperature may be encountered, frostbite may be a factor of even greater importance than the military strategy of the commanders. More than one campaign has failed because of frostbite and trench foot

E. V. Allen and I warned regarding the military importance of frostbite soon after the entrance of the United States into World War II. Our predictions unfortunately proved to be sound but somewhat conservative Estimates of casualties from frostbite and trench foot have ranged from 30,000 to 50,000 combat troops from the U.S. forces alone These conditions also caused heavy losses in the Korean campaign Prevention of frostbite in combat is primarily a command responsibility For example, among troops ordered to discard all equipment except rifles and ammunition as they moved forward and who later were pinned down by enemy fire, casualties from frostbite have been higher than from battle wounds. Extra socks might have reduced the casualties. In Korea, front-line weather stations have been established and troop movements for the first time have been planned according to the predicted weather—a notable advance.

Frostbite encountered at high altitudes may be considered a purer form of the condition, since here exposure to slush and dampness at temperatures near or above freezing for long periods is exceptional

A typical story told by men returning from high altitude missions was that some mechanism, such as a machine gun, jammed and to adjust it the gunner had to remove one of his gloves. Immediately on contact with the metal frostbite developed This is not surprising when one considers that the temperature was frequently 40–60 degrees below zero Early in the war bombing planes commonly had large vents because of "bubbles" which were not properly enclosed and other errors in construction This situation was remedied later and flyers were usually equipped with electrically heated suits. Sometimes, however, a part or the whole

of the heating equipment failed and frostbite followed. As time went on, the incidence of frostbite in high altitude bombing was markedly reduced, except when flak or bullets from enemy planes produced vents in the plane's structure.

Pathology—Exposure to severe cold causes vasoconstriction both locally and as a result of general reactions. This continues for some time. The resulting anoxemia seriously affects the local tissues. In addition, frozen crystals of tissue fluids form, and when these thaw out the cells are ruptured and membranes break down to produce necrosis. Thrombosis of the smaller arteries occurs, increasing the tendency to death of the tissue and gangrene.

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An important element in the production of frostbite in civilian life is peripheral vascular disease. I have seen numerous individuals who were brought to their physicians because of frostbite and

in whom there was evidence of occlusive arterial disease such as arteriosclerosis obliterans or thromboangiitis obliterans or in whom there was definite evidence of Raynaud's syndrome. Patients with any one of these syndromes should take special care to avoid exposure to cold because they will suffer frostbite at a much higher temperature level than will the average normal individual.

Symptoms.—It has seemed logical to classify frostbite according to degree, so that others reading reports of cases may have some conception of their severity. In 1942 Allen and I suggested a classification which follows in a general way that commonly used for burns.

1st degree. This is characterized by the development of a white or yellow frostbite involving the outer layers of the skin without blistering or peeling.

2d degree. Damage to the superficial layers of the skin is severe enough to produce blistering or peeling but not severe enough to affect the deep layers of the skin or the subcutaneous tissues.

3d degree. Damage is sufficient to cause death of thick layers of skin and subcutaneous tissues

4th degree. Gangrene develops, resulting in the loss of an extremity or a portion of it.

In first degree or mild forms of frostbite the skin assumes a dull yellow color associated with numbness and paresthesias over the affected area, for example, the cheek. Application of a warm hand or return of the patient to a normal environment will cause normal color to return. The affected areas, however, remain hypersensitive to further exposure to cold for a period of time, in some cases for years.

With second degree frostbite the onset is essentially the same as in the milder form, but the tissues become firm and digits that are involved become stiff. On thawing, reactive hyperemia develops. With recovery, redness tends to spread from the normal tissue toward the center of the affected area. This is frequently associated with pain, especially of a burning order. Shortly after

edema of the part occurs and blisters are noted (Fig. 82). Portions of the skin then peel off easily. The superficial skin layers may appear necrotic or gangrenous Inexperienced observers often believe the tissue involvement is much deeper than it actually is. Following care the superficial skin peels off, leaving normal tissue

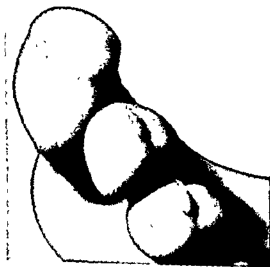


Fig. 82 —Second degree frostbite of left first toe after exposure to —23 F. Note marked blister formation

and frequently entirely normal skin under areas which were thought to be lost.

In third degree frostbite there is more extensive and deeper involvement (Fig. 83), and in the severest forms portions of the limbs and digits may be lost completely

Patients who have suffered from severe frostbite frequently continue to be highly sensitive to cold for many years and should avoid further exposure. This was emphasized during World War II when soldiers were of necessity required to go back into combat after one or more bouts of frostbite It was found that many of

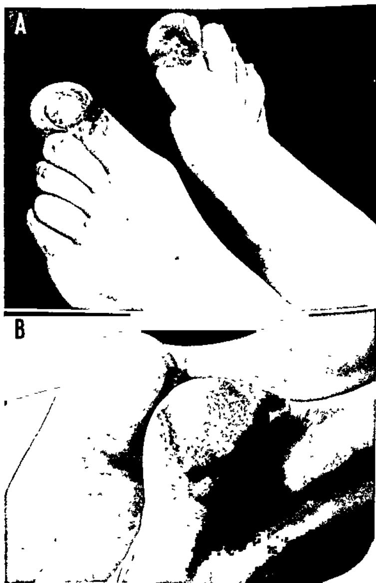


FIG. 83—Third degree frostbite after exposure to —23 F. *A*, involvement of great toes of both feet *B*, frostbite of right heel

them could not tolerate even moderate cold and were quickly incapacitated again

Prophylaxis—In civilian life most frostbite can be prevented by prophylaxis During a war a large percentage of soldiers can be protected against frostbite by prophylaxis, although on some occasions proper protection cannot be instituted.

The following measures for protection are suggested for those who are to be exposed to extreme cold. Clothing should be loose, light, warm and of many layers. The outer layer should be of windproof material such as Grenfell or Byrd cloth Extra supplies of dry wool socks should be available, and double layers of gloves, the outer layer to be windproof, should be worn The best type of footwear is the Eskimo mukluk These boots are made of sealskin with an inner layer of caribou skin. Between the layers of skin, grass or a special type of moss which is common in the Arctic areas or newspaper may be stuffed to increase insulation If this type of footwear is worn and the feet are kept oiled and dry, freezing is highly unlikely Lacking such footwear, large, loose-fitting shoes should be worn over several layers of wool socks The main difficulty with shoes having rubber uppers would be maceration from sweating, leading to dermatophytosis The feet should be washed daily and carefully dried, then oiled, preferably with whale, seal or olive oil Skin lesions should be carefully watched for and treated promptly It is vital that no tight bands be worn and that the shoes not be laced tightly.

Every effort should be made to keep moving; standing for protracted periods is especially bad Contrary to a common belief, beards encourage frostbite owing to moisture from expired air which freezes and tends to cause frostbite of the face

Treatment.—For mild or first degree frostbite, simple placing of a hand over the affected area or exposure to warm environment is sufficient to restore the circulation to normal The application of additional heat should not be considered

In more severe cases, frostbite should be considered an emer-

gency problem. It is important that the skin not be rubbed or traumatized in any way. Snow should not be applied. The patient should not continue walking after the feet have been frozen, unless this is unavoidable. Many patients have been made worse by walking for several miles and then entering an overheated room or placing themselves near a stove If immediate care is not obtainable and if the foot is not too badly involved, it is wise to remove the shoe and sock and place the foot against the skin of a companion as, for example, within his shirt.

If the patient can be removed to a home or to a hospital, care should be taken to warm the extremity slowly and without exposure to heat greater than natural room temperature. The application of excessive heat locally must be avoided. Warm drinks or an alcoholic beverage may be taken once treatment has begun. It is wise to paint the affected area with a mild antiseptic such as a 1 1,000 solution of acriflavine or 1:5,000 solution of Merthiolate.

There is some controversy over whether it is desirable to keep severely frostbitten feet cold for several days or whether they should be warmed gradually but as soon as possible. In my experience rapid warming has increased the pain, and in many instances has caused such excruciating pain that it was necessary to cool the feet again. The best approach to this problem is probably to expose the feet to room temperature. If the patient complains of great discomfort, the feet are overheated, and if the feet appear to be increasingly edematous it may be wise to play an electric fan over them to keep the temperature reduced moderately. Occasionally the application of ice bags may be necessary to reduce edema and severe pain temporarily. This measure should not be continued for a protracted period.

Nerve blocks, ganglionectomy and similar procedures have been harmful rather than helpful in our experience, despite contrary claims by others. Lange and Boyd reported marked reduction of gangrene in animals and man following use of heparin in frostbite, but this is not finally evaluated as practical therapy.

During the Korean campaign a large experience has been accumulated with the use of very dilute infusions of procaine solution. Although the early reports have been favorable, final evaluation has not yet been possible.

Surgeons should restrain any desire to amputate early simply because the entire foot or hand is covered with a black gangrenous layer. Frequently the blackened necrotic skin peels off after a time, leaving normal skin with perhaps loss of portions of one or two digits. *There should be no haste about operating. Every opportunity should be given for the extremity to return to normal status, even if this takes several months.*

Trench Foot

As mentioned earlier, in land warfare frostbite and trench foot are frequently present together to produce a confused picture In some instances, however, true trench foot develops on exposure to a temperature which is higher than that causing frostbite but at which continued exposure to dampness results in trench foot During the military campaigns of the Napoleonic Wars, the Crimean War and World War I there were many thousands of casualties due to trench foot

Etiology.—After interviewing and examining hundreds of patients in the vascular centers of the United States Army during World War II, I was impressed by the similarity of the stories regarding the production of trench foot

Typically the patient was in a combat zone where the temperature was freezing or perhaps even a few degrees above. There was slush or wet mud over most of the area or at least where the particular soldier was stationed In a forward position he was held under fire in a foxhole or trench for 24–48 hours or longer, unable to exercise the lower extremities properly because of the risk of being shot and unable to obtain a fresh supply of dry footwear because of his exposed position

Some of these men were in such situations for more than 10

days, the longest period claimed by any I interviewed being 22 days This soldier was in the hills of Italy. When he was finally able to escape from his foxhole he was unable to walk and had to crawl for 6 miles on his knees. In addition to trench foot he thus developed lesions which were a combination of trauma and a condition similar to trench foot on the anterior surfaces of the knees and which were deep enough to expose the bone.

Pathology.—Examinations of biopsy specimens and amputated tissue have revealed an organization of thrombosed vessels not unlike that encountered in Buerger's disease if the condition is late. Degeneration, ischemic necrosis and infarction are present in both soft tissues and bones and are later succeeded by scarring and atrophy. There are marked phagocytosis of lipids and atrophy of fat in subcutaneous adipose tissue. The muscles show atrophy and ischemic changes similar to those of Volkmann's contracture. Necrosis of bone with sequestration is followed by sheathing of the dead trabeculae with new osseous lamellae, a condition resembling that of Sudeck's atrophy. Friedman has concluded that, at least pathologically, the distinction between true frostbite and trench foot should probably be abandoned since the tissue reactions follow the same general pattern.

Symptoms.—The first symptoms noted by the patient are feelings of coldness, dampness, numbness and "woodiness." As long as the patient remains exposed with his boots on, the feet are to some degree anesthetized from the cold. The pain is not severe. When, however, the patient returns to a warm environment and removes his boots, marked edema develops rapidly and a hemorrhagic extravasation under the skin frequently takes place. The feet become markedly hyperemic and intense burning pain is characteristic. The soldiers discovered that removal of boots in the field was dangerous because of the great risk that they could not be replaced. The inclination, therefore, was to keep the boots on unless rescue was at hand. After the return to warm environment and development of extravasation and edema, gangrene may fol-

low. The gangrene may vary from a few isolated areas of the skin to rather widespread involvement of, for example, both feet. As in the case of frostbite, gangrene is apt to be very superficial. Frequently with gangrene to the ankle, pulsation of the dorsalis pedis artery can be felt.

Any thought of radical excision or amputation early in the course is to be discouraged since observation of large groups of patients many months after exposure revealed that the gangrenous skin usually peels away, leaving normal skin beneath. The number of feet or even of digits lost as a result of pure trench foot was extraordinarily small Secondary infection with both aerobic and anaerobic gas-forming bacteria is a constant risk. A few deaths have been reported as a result of secondary infection

Prophylaxis.—The prophylaxis program suggested in the *Bulletin of the United States Army Medical Department* (p. 1, February, 1945) seems satisfactory.

1. Provision of suitable equipment Well fitting waterproof or water-resistant boots with thick, replaceable, inner felt soles and wool socks may be best under certain conditions. However, with existing footgear adequate protection against trench foot can be achieved by careful observance of the measures listed below.

2. Avoidance of unnecessary risk. (*a*) Standing in water or mud-soaked areas should be avoided as much as possible. (*b*) Cramped positions, prolonged immobility and dependency of the extremities should be avoided. These should be counteracted by stationary exercise of the feet and legs. (*c*) In cold wet weather troops should be relieved of duty as often as the situation permits.

3. Enforcement of individual hygiene (*a*) Wet socks and inner soles should be changed to dry ones as often as possible. Troops should carry a dry extra pair of socks at all times (*b*) Shoes should be removed at least once daily and the feet cleaned and dried. (*c*) The upper part of the body should be kept as warm and dry as possible. (*d*) Noncommissioned officers should be prepared to supervise their men in the care of their feet. Frequent inspections by unit commanders would be valuable in enforcing proper foot hygiene and also in detecting early clinical manifestations when men are exposed to trench foot.

Apart from the provision of equipment, control rests with the individual himself. Measures to be taken are elementary but relatively unfamiliar to soldiers without appropriate precombat training or combat experience in cold wet terrain and they require diligent application to be effective. Otherwise a well conceived and executed control program will be defeated as it sifts down the chain of command unless all echelons enforce control hygienic measures and force the policies of relief and rotation calculated to minimize exposure. Daily foot inspections by commissioned or noncommissioned officers and enforced exercises and changes of footgear exemplify the type of vigorous surveillance which is difficult to insure, yet must be attained, if control is to be achieved

Treatment.—Once the diagnosis has been made the patient should be removed, without walking if possible, to a hospital

In the early stages greatest relief is obtained in most instances by bed rest with the feet elevated and kept cool Later, in *early cases without gangrene,* active and passive movement of the feet is essential. Well fitted shoes must be provided and early walking insisted upon There is some inhibition to beginning walking because of paresthesias, which are most annoying, and this frequently becomes an acute problem with regard to future activity

Hyperhidrosis is often serious to the point where the patient is disinclined to put on socks and shoes which almost immediately become wet. Lumbar procaine blocks and sympathectomies have been used for treatment of the hyperhidrosis. I have had an opportunity to observe the end-results in large numbers of patients thus treated. In most, if not all, instances relief from hyperhidrosis was striking. In some, unilateral sympathectomy was done to permit the patient to evaluate the benefits and to decide whether he would have the other side treated on the basis of the relief obtained Some individuals have elected such treatment of the second side, but the majority have not considered the benefit adequate because relief from paresthesias and other discomforts has not been remarkable. Therefore, if hyperhidrosis and coldness are severely incapacitating, ganglionectomy should be considered. If these factors are not so important, and paresthesias and other discomforts

predominate, there is little use in attempting ganglionectomy for relief. In all cases a procaine block should be performed first to evaluate the potential benefits.

In *severe cases with gangrene* the following treatment has been developed.

1. The gangrenous area is treated with aseptic technic until it has definitely demarcated and appears noninfectious. After that. the need for having the patient begin to bear weight necessitates some decrease in the rigidity of sterility precautions.

2. Typhoid vaccine intravenously to induce fever is helpful in a considerable number of patients. The dosage and technic described on page 201 are satisfactory for this purpose.

3. The results of infusions of dilute solutions of procaine, used in the Korean campaign, are encouraging but require further evaluation.

4. Early ambulation is exceedingly important. Few patients with this condition will, of their own volition, try to walk because of the paresthesias and discomforts already mentioned. Various methods of overcoming this inhibition were utilized in the Army vascular centers These included many types of exercises which did not require weight-bearing on the feet and which were intended to improve the general physical stamina. Among others were the riding of bicycles to encourage pressure on the toes and exercising in swimming pools where the buoyancy of the water lessened the weight on the feet until they became accustomed to walking. An anterior bar was designed which could be placed on the soles of the shoes and would prevent the ball of the foot from coming in contact with the surface on which the patient was walking.

At this point it is perhaps appropriate to describe the characteristic walk of the patient with trench foot. Because of the discomfort, which is largely concentrated in the balls of the feet, the patient walks with a sort of duck waddle, resting back on the heels and avoiding pressure on the balls of the feet. This means that the

toes are thrown conspicuously outward. The walk is so characteristic that an observer who has had experience with the late effects of trench foot readily recognizes the condition in an individual walking some distance from him.

5 As the tissue demarcates and the skin becomes loose it is carefully removed. Amputation is reserved for only the tips of digits or for entire digits that are really involved beyond hope

6 Skin grafting is frequently useful in areas that have been severely involved.

Immersion Foot

Immersion foot is, in many respects, like trench foot. It is the result of prolonged immersion in water as, for example, in individuals who have spent days on life boats or rafts as a result of shipwreck. This, again, is primarily a wartime condition, although it does happen in peacetime. It may occur in warm climates as well as cold, although most of the cases described have followed exposure in cold areas, as in the North Atlantic.

Etiology —The following factors are the same whether immersion is in cold or warm water prolonged dependency of the lower extremity, prolonged immobility; frequently, a binding constriction of the leg, lack of proper food, with low protein and vitamin intake, with vitamin B complex appearing to be the most important; maceration from prolonged soaking The only differences are exposure to cold and cold water and exposure to warm water and the effects of sunburn.

Clinical picture —This has been divided into three phases: (1) the initial or spastic ischemic phase; (2) the postimmersion, hyperemic stage, and (3) the late vasospastic, ischemic phase. For a detailed description of this syndrome we are indebted to Blackwood, and White and Warren and others.

During the period of immersion there is a direct vasoconstriction of the superficial arteries and arterioles plus a reflex vasoconstriction affecting the circulation generally. The extremities

become pale or cyanotic and cold. Pulsations are reduced or absent because of vasoconstriction. Edema appears within 12–24 hours as a result of dependency and interferes further with the normal circulation Petechial lesions are apt to appear, especially in persons exposed in warm climates. Shallow ulcerations may develop over the ischemic area. Anesthesia becomes prominent. In warm climates sunburn with the development of blebs is very common.

The postimmersion hyperemic phase occurs when the patient has been removed from cold and placed in a warm environment. The feet become more swollen, red and hot and the peripheral pulsations are full and bounding. Sweating is not noticeable. The feet must be immediately elevated and placed in a cool environment or there will be a pronounced increase in the swelling and hemorrhagic blebs will appear. In many cases ulceration and gangrene may occur. Anesthesia and numbness may persist for a few days, but later burning paresthesias develop and become more intense as the days pass. This phase may last for several weeks or longer Secondary infection is relatively common unless guarded against and thrombophlebitis has been seen.

The late vasospastic ischemic phase is seen in severe cases weeks or months after the acute phase has passed. The extremities are cold and cyanotic and the patient complains of pains, stiffness and paresthesias of the lower extremities. Hyperhidrosis may then appear. This syndrome may continue or reappear during cold weather for some years after the original insult and may interfere with the patient's livelihood if he is an outdoor worker.

Prophylaxis—The *Bulletin of the United States Army Medical Department* (February, 1945) contained the following suggestions for the prevention of immersion foot

1. If there is time before abandoning ship, try to obtain warm clothes and warm covering (oil skins, rubber sheets, canvas), waterproof and loose fitting boots and several pairs of wool socks.

2. Keep the feet and bottom of the boat as dry as possible. Even when boots are worn, prolonged contact with cold water is harmful.

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3. If socks become wet they should be removed. The feet should be dried and oil, petrolatum or heavy grease applied if possible. Boots and socks should be well dried before being replaced.

4. Avoid cramped positions and dependency of the extremities by frequent exercises and temporary elevation of the feet.

5. Keep the upper part of the body dry and diminish exposure to cold winds.

6. Constriction by tight clothing, shoes, socks and garters should be avoided.

7. Nutrition should be maintained at as high a level as circumstances permit. Whisky and other alcoholic beverages should be avoided

It is obviously impossible in many circumstances to follow in detail such directions as these. They should, however, be applied whenever and to the degree feasible.

Treatment.—When the feet are severely involved, the patient should be lifted or carried from the lifeboat or raft if possible This will decrease the rubbing of injured skin under potentially septic conditions. An extremely warm environment should be avoided. The feet should be elevated and kept moderately cool in a cool environment or, if necessary, with ice bags or a spray of water over the skin Cooling may be helped by means of a fan directed toward the affected area.

All possible precautions should be taken against bacterial contamination. A mild antiseptic such as acriflavine, Merthiolate or one of the sulfonamides may be applied to areas where the skin is broken. A wet dressing of penicillin, 10,000 units per 250 cc of normal saline, may be used if infection is present and if the organism responsible is susceptible to penicillin. Penicillin or one of the sulfonamides should be administered orally or parenterally if there appears to be a generalized infection. Heat and strong antiseptics should never be applied to the skin of the affected areas

As soon as the swelling has subsided and does not recur on de-
and provided the ulcerations are healed, the patient
encouraged to become ambulatory and to place his
the soles of his feet. Paresthesias present in immersion

foot are of the same order as those described for trench foot. If a patient has had serious involvement of this nature, he should attempt to find an indoor occupation since he is quite likely to have serious disability or at least discomfort on exposure to cold.

Sympathectomy is not indicated because the swelling and symptoms are frequently aggravated.

The Pernio Syndrome

The pernio syndrome should be divided into the acute form, or acute chilblains, and the chronic form, or chronic chilblains. Acute chilblains may be regarded as the very earliest stage of acute frostbite, and chronic chilblains may be considered mild chronic frostbite. Certain aspects of pernio, however, deserve special attention Immersion foot and trench foot may be considered related conditions.

W Müller wrote a small monograph on pernio, *De pernionibus*, in 1680, and a number of works on this subject have appeared since that time McGovern and I emphasized that pernio is a peripheral vascular disease rather than a dermatologic one.

Acute Pernio (Acute Chilblains)

This is relatively common in northeastern United States and in many other cold and damp climates. It is frequently seen in the hands of outdoor workers and of young children who have been playing in the snow. It is also seen with increasing frequency in the legs of women who wear short skirts, thin stockings and inadequate shoes in winter weather.

The nose, cheeks and ears are rarely involved. The lesions are almost always bilateral and symmetrical. The patient complains of an itching, burning sensation which is severely aggravated by warmth, on coming indoors after exposure to cold. Washing the affected parts in warm water after exposure to cold aggravates the discomfort. The skin is reddish and sometimes has a cyanotic tint.

There is usually slight edema. Sometimes small blebs appear If there is no further exposure to cold the condition gradually subsides in seven to 14 days. Occasionally there is a purpura-like reaction during the acute stage, and at times a brownish pigmentation persists for several weeks thereafter. Occasionally the skin becomes roughened, and frequently a diagnosis of dermatitis secondary to exposure to some substance to which the patient is hypersensitive is considered.

Treatment —Exposure to heat greater than 85 F is undesirable. Trauma, including scratching of the area, must be prevented. If blebs break they should be treated in an aseptic manner, using a mild antiseptic and sterile bandage. Salves, ointments and strong antiseptics are contraindicated. The old idea that the lesion should be rubbed vigorously with snow should be discouraged, for the brisk rubbing may traumatize the skin and aggravate the condition generally and may induce mild frostbite. Acute pernio is not a serious condition and will yield to reasonable care. Further exposure to cold without proper protection must be avoided Repeated or prolonged exposure may result in chronic pernio, which is a much more serious condition

CHRONIC PERNIO (CHRONIC CHILBLAINS)

After repeated exposure to cold and dampness a susceptible person may develop the clinical picture of chronic pernio. The mechanism of the susceptibility is not understood. The condition has been known by a wide variety of names, including Bazin's disease, dermatitis hiemalis, lupus pernio and erythrocyanosis. Some of the confusion resulted from Bazin's writings in which he described cases under the heading of erythema induratum which were in truth pernio rather than a true tuberculid One reason for his confusion was that the bacteriology of tuberculosis had not been worked out at the time he wrote. Careful review of his original articles, however, shows that several of his patients had lesions that were characteristically located and that occurred during the

winter and cleared up each May or June. Furthermore, his descriptions were accurate pictures of pernio lesions.

Typically, after a susceptible person is exposed repeatedly to cold and dampness, erythematous ulcerative hemorrhagic lesions develop in the skin of the feet and legs, usually below the knee. The great majority of patients we have seen have been young women The explanation which suggests itself is that the thin stockings worn today fail to give adequate protection against dampness and cold during the winter months. It is interesting that in some of the older German descriptions the lesions were reported as rarely occurring on the legs and feet, being more common on the face and hands. This adds weight to the foregoing hypothesis, since at the time of the early reports German women wore long heavy underwear, heavy stockings and high shoes and hence their lower extremities were not especially exposed to the cold and dampness.

During the early years of the disease in a given patient the lesions usually appear as small nodules in October or November and break down in three or four weeks into open and extremely painful ulcers. The ulcers usually persist through the winter and finally heal in the late spring or early summer. They leave permanent scars and the legs of patients who have had this disease for years are disfigured permanently by numerous pigmented scars. The lesions vary from pinhead size to several centimeters in diameter As the condition progresses the lesions may remain open throughout the summer. They may be so painful as to be completely crippling I have seen several individuals who had been bedridden for several years as a result of the extreme pain Some lesions may heal during the winter; as one ulcer heals others break open so that there are successive crops. Most cases are incorrectly diagnosed because sufficient attention is not paid to the influence of exposure to winter weather and the tendency toward healing in the summer. This series of events alone should give the physician a clue to the diagnosis.

Most patients are found to have a lower normal skin temper- ture than the average person. The extremities are cool and fre- quently cyanotic. Local edema is often present around the ankles. In some individuals livedo reticularis is present and, as noted in Chapter XIV, the pathologic process in the blood vessels in the two conditions is somewhat difficult to differentiate. Characteristi- cally lesions are seen simultaneously in several stages of develop- ment, ranging from tender erythematous nodules, through the small bleb phase to superficial ulcers. Later the ulcers becom deeper. They may be round or completely irregular in shape. Th edges are usually sharply demarcated. There is moderate indura tion surrounding them. Biopsy reveals angiitis associated with low grade inflammation in the subcutaneous tissues.

As emphasized by McGovern and the author, the patholog picture is characteristic of, but not specific for, pernio. Simil pathologic lesions have been observed in acrocyanosis, lived reticularis and some cases of trench foot. They have three featur in common: (1) angiitis with intimal proliferation, thickening the wall of the artery, with periarterial-perivenous infiltration b lymphocytes, monocytes and leukocytes; (2) necrosis of the pa niculus adiposus; (3) chronic inflammatory reaction of the su cutaneous tissues in which giant cells are frequently found b tubercles never. Purpuric areas are common. In some cases the is hyperpigmentation. No acid-fast bacteria or true tubercles a found.

The mechanism is probably based on repeated vasospastic r actions producing anoxemic changes in the tissue. The followi cases are illustrative of the typical syndrome.*

Case 2.—A girl, 19, was first seen in April, 1938. After injury the right leg in March, 1937, she had noted red blotches that were el vated above the surface which first appeared on the back of the low third of the leg. The lesions became more raised and scaly, then a

* Originally reported in McGovern, T., and Wright, I. S.: *Pernio: A vascu disease*, Am. Heart J. 22:583-605, November, 1941

peared to come to a head, ulcerate and heal. After two weeks in bed the red blotches remained and similar lesions appeared on the left leg. During the summer the lesions healed. In November, without new injury, several similar lesions reappeared, each developing into an ulcer No treatment was instituted. In May, 1938, all lesions disappeared. After a slight injury to the right leg in December the condition returned and both legs ulcerated Late in the summer of 1939 the lesions had not completely healed but were improved and confined to the lower third of the legs along the medial and posterior surfaces.



Fig 84—Pathology of chronic pernio Note hyperkeratosis and abscess

When the lesions began to appear they were excruciatingly painful; after ulceration set in the pain was less acute.

Physical examination in April, 1938, showed no abnormality except the leg lesions Blood pressure was 100/50. Oscillometric readings and capillary studies were normal Roentgen study of the lungs revealed no abnormality. The Mantoux reaction was positive at 1 1,000

Biopsy of a lesion revealed no evidence of tuberculosis Except for a small zone of ulceration, the overlying squamous epithelium was not abnormal. Immediately beneath the basal cell layer was an extensive leukocytic reaction that diffusely infiltrated the subcutis. Capillaries in this region were unusually prominent as a result of endothelial and pericapillary fibroblastic proliferation The panniculus was extensively necrotic, containing many nuclear fragments but showing no true caseation (Fig 84) Polymorphonuclears and small lymphocytes infiltrated the adipose tissue and there was considerable fibrosis The most conspicuous feature in the panniculus was the vascular change, which con-

sisted of chronic angiitis; not only was the endothelium greatly thickened but there was a striking perivascular ring of fibrous tissue containing many cells, chiefly of the lymphocyte series.

Case 3.—A woman, 39, was first seen in September, 1938. The history was insignificant except for the following events In October, 1937, she had had an eczematous condition that involved the flexor surfaces of the legs, back and hands, in that sequence. Roentgen therapy was given. The condition, of unknown etiology, had cleared up in 10 weeks At age 14, red indurated areas which were painful on pressure developed on the inner and posterior aspects of both legs. They became inflamed and healed without ulceration. In the fall of her eighteenth year similar areas appeared and this time ulcerated. For the next seven years the legs were normal. At 25, the lesions recurred after swimming late in the summer The condition was such that she was in bed most of the time from October until June, wearing a gelatin boot that was changed frequently. The legs healed and she remained well for three years For the following 11 years the right leg had never completely healed, although it was definitely improved during the warm months. The left leg had been free from ulceration for four years.

In October, 1938, she had excruciating pain across the right instep and ulcers appeared between three toes of the right foot. Ulcers then developed on the dorsum of the foot and a single large lesion persisted The pain in the reddened areas was knifelike. The areas were discrete and the color changed from red to violaceous When the patient opened the lesions with a needle, dark red serum exuded for a day, then yellowish serum, and the lesions began to ulcerate, with cessation of pain. The ulcers healed in four to five weeks. The healed areas were deeply pigmented, and on these the next year's crop of lesions became engrafted The lesions were open almost all winter and she was confined to the house from October to the end of February.

Physical examination revealed no abnormalities except the leg lesions The skin was deeply pigmented and sclerodermic from the knees down. A large ulcerated lesion was present on the internal malleolus and another on the dorsum of the right foot The left leg showed pigmentation, scleroderma and evidence of healed ulcers Oscillometric readings were normal. Lung x-rays showed an old inactive tuberculous focus in the right hilus and an old Ghon nodule. The sputum contained no tubercle bacilli; the Mantoux reaction was positive at 1:1,000

Biopsy of a lesion showed no evidence of tuberculosis. There were extreme hyperkeratosis and a fairly large abscess in the squamous

epithelial layer (Fig. 85). This represented a long-standing chronic process in which ulceration played a conspicuous role, indicated by the fact that nests of epithelium lay in isolated foci in the subcutaneous connective tissue. The angiitic reaction in the subcutis was conspicuous. The vessel walls were greatly thickened, in some instances almost to the point of complete occlusion of the lumens. Each vessel thus involved was surrounded by collections of neutrophilic leukocytes, lymph-

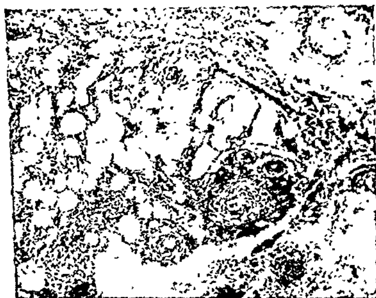


Fig. 85.—Pathology of chronic pernio. Panniculus is extensively necrotic, capillaries are unusually prominent. Leukocytes and small lymphocytes infiltrate the adipose tissue. Note endothelial thickening and perivascular ring of fibrous tissue.

ocytes and large mononuclear cells. There was extreme necrosis in the panniculus adiposus, some of the necrosis even suggesting caseation. Chronicity was indicated by extensive granulation tissue on the margins of the necrosis. An interesting feature was the presence of many cells in division, both in the involved vessels and in the dermis.

Case 4.—A woman, 39, had had two miscarriages and one full-term pregnancy, the latter 10 years previously. In September, five years before admission, she first noted cold, itchy feet, followed shortly by blistering,

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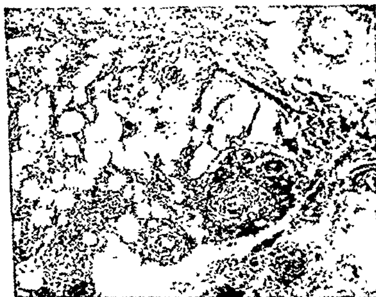


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with ulceration of the inner surface of the left ankle. Each summer the lesions healed but reappeared in the fall. The ulcers were treated by salves in a skin clinic.

On exposure to cold the patient had a burning feeling followed by itching, which was a sign of initiation of the leg lesions The areas

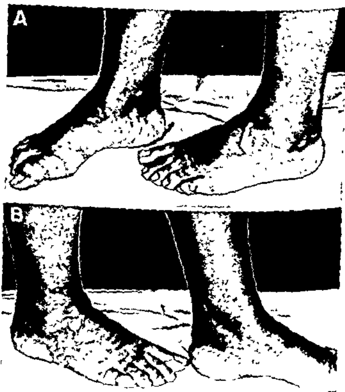


Fig. 86.—Chronic pernio. Leg and ankle lesions, with numerous small ulcers and scars with pigmentation.

became bluish red and some even suggested subcutaneous hemorrhages. *Size varied from* a petechial spot to that of a dime. There was severe *knifelike pain,* worse at night, in the discolored areas. After two days *to three weeks* a blister would form, exuding pinkish or yellowish exudate, followed by *ulceration.* A scab would form and the lesion heal. At this stage, any injury to the legs by exposure or otherwise caused the

lesions to ulcerate again. Each crop of lesions usually began simultaneously. They were confined to the legs, usually the lower third, with a few lesions on the dorsum of the foot and toes. The severe pain usually lasted until ulceration, then progressively diminished.

Physical examination showed no abnormality except the leg lesions There were large square granulating lesions on the inner aspect of the ankles extending back to the calves and marked ulceration of the ankles, backs of the feet and the toes (Fig. 86) The dorsalis pedis and posterior tibial arteries were normal. There were no color changes in the feet on elevation or dependency. There were slight varicose veins in both legs Oscillometric readings were normal. Lung x-rays revealed no abnormality All cold sensitivity tests gave negative results

Biopsy of a lesion revealed no evidence of tuberculosis There were superficial cornification and exfoliation of the stratified squamous epithelium and an increase of fibrous tissue in the underlying corium, with marked edema and smoothing of the rete pegs. The sweat glands were displaced and their coils separated by the increased, edematous connective tissue fibers Mild mononuclear cell infiltration was noted The deeper layers of the epidermis were pigmented and lymph spaces were dilated, with a tendency to vesicle formation The capillaries showed evidence of proliferation In the subcutis the vessel walls were greatly thickened, occluding the lumens, and there was marked perivascular infiltration. The striking feature was angiitis

Differential diagnosis must include erythema induratum (true Bazin's disease). The lesions of erythema induratum are apt to be more nodular and indurated and the late ulcerative lesions are likely to be deeper Occasionally seasonal changes are noted. Tubercle formation and caseation are found Pernio must also be differentiated from erythema nodosum, which is a much more acute process and is usually associated with acute systemic reaction, with fever, malaise and sometimes arthralgia. It usually occurs in the spring and fall rather than in the late fall. The lesions do not tend to ulcerate. The third consideration in differential diagnosis is nodular vasculitis The lesions are extremely painful and usually occur in the calves of women between 30 and 40 years of age. Ulceration is rare.

Treatment—There is no specific treatment for chronic pernio.

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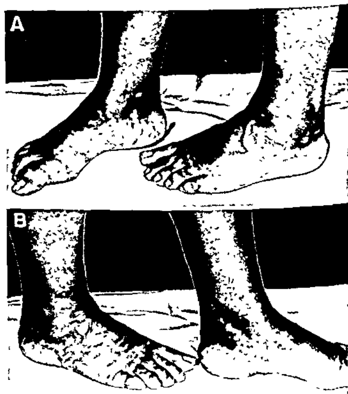


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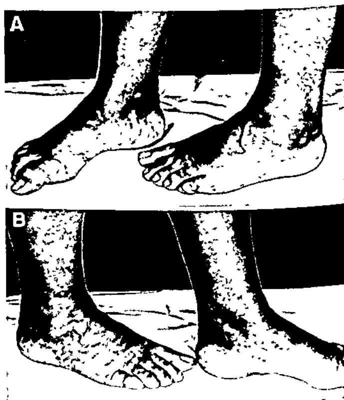


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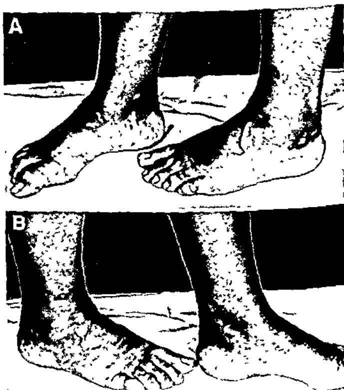


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been tried without impressive results. We are now studying the effect of ACTH and cortisone in the treatment of superficial ulcers of this character and the results seem encouraging, but it is too early to draw final conclusions regarding their worth

CRYOGLOBULINEMIA

Among the more interesting conditions which may simulate thrombosis but concerning which there is no evidence that the true mechanism of thrombosis is involved are *cryoglobulinemia* and the syndrome of cold hemagglutinins In both of these conditions the blood may become thickened to the point of obstructing —interfering with the circulation through the minute vessels, producing secondary infarction and, in severe cases, gangrene of the tissues

The cold-precipitable proteins of cryoglobulinemia are encountered most commonly in multiple myeloma and kala-azar but may also be seen with arthritis, hepatic disease, disseminated lupus and, rarely, other diseases They may be present in some, but not the majority of, patients with Raynaud's syndrome

Although the occurrence of cold-precipitable agglutinins in the serum or plasma is not rare, the presence of clinically significant amounts has been recognized in only about 15 cases

Characteristically there is difficulty in withdrawing blood samples and carrying out laboratory procedures with the blood because when its temperature falls below 37 C the cells agglomerate and become enmeshed in a precipitate of cryoglobulin. Warming to above 37 C generally produces resolution of the precipitate and freeing of the cells Although the temperature of the central areas of the human body (e g , rectum) tends to remain above 37 C , it is not uncommon for the temperatures of the peripheral and superficial areas to fall far below this critical point on exposure to low environmental temperatures or during such common acts as the handling of ice It is not surprising, therefore, that in such circumstances sludging, precipitation and obstruction of the vessels

Above all, the patient should be protected from exposure to cold and damp. Living in a warm climate often prevents the recurrence of lesions, and if this is done in the early stage of the disease the prognosis may be rather good Moving into the northern part of a warm zone is not always sufficient protection I have had patients move as far south as the Carolinas without satisfactory response, and in Texas, where a cold wind may blow for a day or two, the lesions may become active, although less troublesome than in a northern climate.

Healing has been reported following various forms of therapy, but because successive crops of lesions tend to heal, evaluation is difficult. We have used Mecholyl ion transfer triweekly with adequate protection of the legs from cold In other patients artificial fever therapy by means of typhoid vaccine intravenously has been associated with rapid healing The object of this procedure is to induce vasodilatation in order to improve the supply of blood to the ulcerated area.

Four of our patients have had lumbar ganglionectomies. The immediate response was rapid healing of the lesions, possibly owing to the vasodilatation associated with the anesthesia and complete rest in the protected environment of a hospital for several weeks. The ganglionectomy undoubtedly aided in the vasodilatation After following these patients for several years, however, there is a question whether ganglionectomy has produced striking permanent results. One patient had a ganglionectomy performed on one side as a test, then elected to have one on the opposite side the following year in the belief that she had improved sufficiently to warrant the second operation. She has, however, continued to have ulcerations during the cold weather of each winter. It will be necessary to follow a larger group of patients who have had ganglionectomies before final conclusions can be drawn regarding the procedure. If the patient has a severe crippling and progressive form of chronic pernio, it would seem worth a trial at this time

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may occur. If this persists over long periods, infarction and gangrene may result. In one case to be reported by Dr. David Barr, the tissue damage was of such an order that gangrene of the fingers, toes, nose and ears occurred.

Cold Hemagglutinins

Cold hemagglutinins have been reported in low titer in the serums of patients with a great variety of diseases and in normal individuals. Those found in human serum characteristically act specifically on sensitive cells, of the patient or of other individuals The reaction of clumping of the cells is precipitated by cold, even at room temperature, and reversed by warming to body temperature McCombs and McElroy first reported gangrene produced by the obstructive action of cold hemagglutinins in 1937. Since then other reports of gangrene of the extremities on this basis have appeared In several cases hemolytic anemia accompanied the phenomenon.

The obstruction appears to be due to mechanical blockage produced by masses of cells in clumps and rouleaux acting much as a log jam as the arterial tree becomes progressively narrower No cryoglobulins are involved, although doubtless these two phenomena and thrombosis in the classic sense have been confused in the past. The agglutination produced by cold hemagglutinins does not involve the constituents of the blood in the true thrombosing process. Mere warming of a test tube in which the phenomenon of cold hemagglutination has taken place reverses the process In man, however, if ischemia of tissue caused by this phenomenon persists for a sufficient length of time, the processes of necrosis will proceed, with loss of tissue.

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CHAPTER XIV Livedo Reticularis (Cutis Marmorata)

LIVEDO RETICULARIS or cutis marmorata is characterized by a marble-like mottled discoloration of the skin, which is usually dusky red or slightly bluish. The condition has been described by several terms, including livedo racemosa, livedo annularis and asphyxia reticularis

The mild form is very common. The mottling disappears when the patient comes into a warm environment, and most patients pay little or no attention to it The mild cases fall in group I of Williams and Goodman's classification They classify group II as livedo reticularis idiopathica, in which the bluish-red mottling is more intense than in group I and persists despite the patient's being brought into a warm environment. These two groups probably differ only in degree and represent essentially the same condition. Group III represents livedo reticularis associated with some other skin or subcutaneous vascular disease such as erythema induratum, essential polyarteritis, syphilis or pernio.

Etiology.—The etiology of livedo reticularis is unknown. By far the majority of patients have been girls and young women under 40 The rarity of the disease in women over 40 has raised the question of what becomes of the condition with aging. So far as I know, a significant group of cases has not been followed for a sufficient number of years to give a clue. It would be interesting to know whether the patients tend to develop other vascular dis-

eases such as varicose veins or whether the condition clears up permanently. Craig, Hines and Barker reported that 30 per cent of their patients had hypertension and in 50 per cent nervous instability was striking. We have not found as high a percentage of hypertension in our cases. The incidence of nervous instability is confirmed in my experience, although the fact that the disease occurs so often in girls and young women, who frequently become acutely conscious of the discoloration of their legs, would probably not make such a correlation remarkable.

Pathology.—The color change appears to be associated with a narrowing, either functional or organic, of the arterioles and conspicuous dilatation of the capillaries and venules.

Craig, Hines and Barker reported pathologic studies made in one case. There was proliferation of the intima and isolated arterioles and small arteries. Some of the arteries were completely occluded and similar lesions were found in some of the larger veins. In many sections, however, the only change noted in the arterioles of the skin underlying the livid parts was a slight thickening of the muscular coat. Some observers have found proliferation of the intima of the arterioles, perivascular infiltration and perivascular fibrosis. Barker's presentation of the report of these pathologic findings followed that by McGovern and me on the pathology of pernio on the same program of the American Heart Association. The similarity of his slides and ours was striking. Except for the ulceration of pernio, the pathologic process of the two conditions appears to be almost identical. Thus, once again we have an example of a vascular lesion which is characteristic of, but not specific for, a given disease.

Clinical picture.—Most patients have no symptoms whatever. They note the increase in discoloration on exposure to cold and an improvement in warm weather. Those with more severe cases complain of color changes, coldness, numbness, aching and paresthesias of the feet and legs. Discoloration is often found also in the palms of the hands and in the skin of the forearms, arms and

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pectoral areas. Allen, Barker and Hines reported recurrent ulceration of the skin of the legs, with occlusion of the arteries of the toes and gangrene. We have encountered five cases of ulceration associated with livedo reticularis Ulceration is, however, statistically rare.

Treatment.—Since the only effect of the condition in most patients is cosmetic and since the etiology is not understood, no specific therapy has been developed The color changes are reported to have disappeared or improved following sympathectomy,



FIG 87—Long standing livedo reticularis in woman, 29, with ulcerations intractable to all treatment, including sympathectomy Histologic studies showed only the characteristic but nonspecific changes of livedo reticularis (From Medichrome Series MM—Vascular Diseases, by I S Wright and W T Foley)

but it is doubtful that this procedure is necessary in most cases since the course is usually so benign Allen, Barker and Hines reported some benefit from lumbar sympathectomy when the condition had progressed to the point of gangrene of the toes In one case there was temporary improvement, then the condition progressed and eventually amputation of both legs was necessary. As far as I am aware, this is the only case on record in which authoritative students of the disease believed amputation was required as the direct result of livedo reticularis

I have seen three patients with severely painful, multiple ulcerations of the toes, feet and lower halves of the legs associated with

livedo reticularis and not explainable on any other basis. The ulcers have been demarcated and usually shallow (Fig. 87) Serosanguineous and purulent drainage was common. Their incidence has not been seasonal. No form of treatment, including sympathectomy, has had any permanent effect ACTH and cortisone are now being tried and do appear to encourage epithelization The dosage has been 25 mg four times a day for seven to 10 days, then reduced to 25–50 mg. a day.

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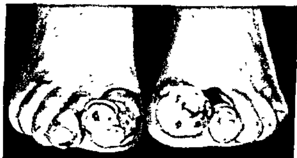


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I have seen three patients with severely painful, multiple ulcerations of the toes, feet and lower halves of the legs associated with

terioles and the venules and edema of the skin and subcutaneous tissues. The capillaries are usually dilated. Thrombosis of the vessels is occasionally present. There is a tendency to slight proliferation of fibroblasts around the involved vessels The endothelium of the vessels may also tend to proliferation, but this is seldom marked Atrophy of the subcutaneous fat in the involved area is not uncommon

Clinical manifestations.—The nodules appear in various arrangements, usually *bilaterally*. *They vary from 1 to 10 cm. in* diameter They are most common on the legs, thighs and arms, less common on the trunk and rare on the hands and face. Typically, they appear on the anterior surfaces of the legs, in contrast to the lesions of erythema induratum which most frequently develop on the posterior surfaces. The nodules are firm, usually painful, tender on palpation and vary in color from pink to cyanotic purple The larger and more chronic ones are likely to be more cyanotic A crop of lesions usually subsides in 10–14 days, but if the causative agents remain in the system, successive outbreaks occur The total anticipated duration is usually three to eight weeks, although it occasionally is considerably longer Recurrence is relatively rare unless the toxic factor is not eliminated There is often a persistent purpuric appearance which subsides slowly, usually leaving brownish pigmentation of moderate degree

The lesions do not suppurate or ulcerate as do those of erythema induratum, pernio and other nodular diseases of the lower extremities. In the cases associated with infection there may be systemic reactions, including sore throat, joint pain, general malaise and low grade fever.

The condition must be differentiated from pernio, in which the nodules characteristically break down into ulceration and which has a seasonal incidence; from erythema induratum, which also tends to ulcerate and ordinarily occurs on the posterior surface of the extremity; from thrombophlebitis, which *usually produces* more elongated lesions, from nodular syphilids, which are more

CHAPTER XV Erythema Nodosum

ERYTHEMA NODOSUM is an inflammatory vasculitis which chiefly involves the skin and subcutaneous tissues of the extremities. It is nonsuppurative and nonulcerative. Females are more susceptible than males, the ratio of incidence being about 4 1. It may occur at any age but is most common in the second and third decades.

Etiology—The vascular reaction may occur under numerous conditions and is probably nonspecific It has generally been considered to be a response to the infection of rheumatic fever or an allied condition, and rheumatic fever is frequently diagnosed when it is present in the absence of other evidence of rheumatic fever. Admittedly erythema nodosum is often associated with rheumatic fever In recent years, however, I have found it more frequently associated with the ingestion of drugs by sensitized individuals. It has followed the ingestion of various barbiturates, salicylates, bromides and sulfonamides, and no doubt numerous other drugs and foreign substances are capable of producing it. It is also associated with measles, diphtheria, tuberculosis, erysipelas and similar conditions. In these diseases it is probably confused at times with reactions to therapeutic agents In view of its occurrence on drug ingestion, it probably should not be considered purely a bacterial or viral condition, and we incline to the theory of localized sensitivity of the connective tissues, including blood vessels, to a bacterial or chemical toxin.

Pathology.—The condition is characterized by the accumulation of neutrophilic leukocytes and lymphocytes around both the ar-

CHAPTER XVI Erythema Induratum

ERYTHEMA INDURATUM is another form of nodular vasculitis. Originally it was thought to be of tuberculous origin, but a tuberculous and a nontuberculous type are now known The tuberculous type is usually found with active tuberculosis, most often accompanying tuberculous lymphadenitis but sometimes pulmonary and genitourinary tuberculosis Tubercle bacilli are seldom demonstrated in biopsy specimens, principally because usually only several sections are studied When a large number of sections from several biopsies are studied, the incidence of positive identification of Mycobacterium tuberculosis is increased In the presence of known active tuberculosis elsewhere, the diagnosis of tuberculous erythema induratum is most likely

There is no known etiologic cause for erythema induratum in the absence of tuberculosis Repeated cultures have failed to reveal any specific organisms from these lesions.

Pathologically the lesions consist of definite proliferation of endothelium and fibroblastic cells There are destruction of the elastic and collagenous fibers and atrophy and necrosis of fat Giant cells are frequently seen in the tuberculous lesions. Small blood and lymph vessels show definite endothelial proliferation, and collections of lymphocytes and plasma cells are seen throughout the sections Fibroblastic proliferation is definite. Necrosis may involve the medial coats of the vessels and there may be necrotic areas throughout the skin and subcutaneous tissues Occasionally the vessels contain thrombi.

often unilateral, and from chronic nodular nonsuppurative febrile panniculitis (Weber-Christian disease), which is a chronic low grade disease involving the subcutaneous fatty tissues and small vessels, is far more chronic, recurs over a period of years and is accompanied by more persistent fever.

Treatment —There is no specific therapy for erythema nodosum. It is considered advisable that the patient remain in bed and apply warm moist packs to the lesions. The administration of salicylates is advocated, and is probably justified, in cases associated with rheumatic fever, but it should be borne in mind that an indistinguishable reaction may follow the administration of salicylates, hence their continued administration in these particular cases is contraindicated One should always search for other manifestations of one of the generalized diseases mentioned previously, especially for rheumatic fever.

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Characteristically, subcutaneous and cutaneous nodules develop on the legs, usually on the posterior surfaces, and occasionally on the arms. The nodules vary in size from 1 to 8 or 10 cm. The color ranges from light red to cyanotic. They usually occur in groups which may become confluent as they enlarge. The lesions, usually painful and tender, are frequently chronic and may exist for many years, with necrosis and ulceration the prominent features The frequent ulceration and slow healing resemble the course in pernio, but there is no seasonal incidence. As one group of lesions slowly heals, successive crops may appear Frequently this condition becomes very serious and on rare occasions the major arteries may be involved with actual occlusion. Allen, Barker and Hines have mentioned a young woman in whom occlusion occurred, followed by gangrene and slough of all the toes of both feet, but this is very rare indeed

There is no specific therapy for erythema induratum. Prolonged rest in bed with elevation of the legs and the use of warm moist packs appears to be helpful. There is a tendency to recurrence and to the development of new crops of lesions with secondary development of orthostatic edema as soon as the patient becomes ambulatory again

Streptomycin in the treatment of these lesions might theoretically be of some value but its effect has not been determined. Removal of foci of infection has been recommended, but the direct relationship has not been established very conclusively.

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CHAPTER XVII · Acrocyanosis

SOME PHYSICIANS confuse acrocyanosis with Raynaud's syndrome. Although the two conditions have some common characteristics, such as blueness of the extremities in response to cold, they differ in important respects For example, in acrocyanosis there are absence of the characteristic Raynaud attacks and presence of excessive sweating and frequently of edema There is also a difference in sex distribution and other factors. It is wiser, therefore, to distinguish the two conditions and to study their differences carefully.

ETIOLOGY

Many etiologic theories have been suggested, and the following seem worthy of consideration.

Cold —Cold seems to be a fairly universal factor in precipitating attacks in susceptible individuals, whereas heat relieves them Cold may be considered the most important external factor, but it cannot be the sole cause or the disease would be more universal in persons exposed to critical low temperatures I have, however, seen many persons who suffered from frostbite or trench foot during World War II in whom there ultimately developed a syndrome indistinguishable from acrocyanosis. How long it will persist remains to be seen, but in some it is present seven years after the severe exposure. In many patients the syndrome has slowly subsided

Mental and nervous disorders.—Acrocyanosis, while relatively unknown among phlegmatic, stable individuals, is common among psychoneurotic patients and is frequently seen in those with neurocirculatory asthenia It is very common among patients with mental disease. In one series reported from England approximately 45 per cent of 110 patients with mental disorders had acrocyanosis. Many patients with identical types of disorders did not have this syndrome

Activity.—Acrocyanosis occurs about 2½ times as often in mental patients who habitually stand or sit around indifferent to chilling as in the normally active patients. While following such groups for four years, Stern observed that 26 per cent showed decreased activity leading to greater cooling of the extremities and increased cyanosis; 12 per cent showed increased activity with consequent warmth and less cyanosis. The rest showed no changes either way.

Endocrine function and sex.—The endocrine relationship is a subject of considerable debate We cannot test completely the activity of many of the endocrine glands I have encountered a number of endocrine dyscrasias in my patients with acrocyanosis and have found basal metabolic rates generally to be in the low normal or slightly subnormal range

The sex ratio is about equal, in contrast to that in Raynaud's syndrome, which occurs more frequently in females than in males In most patients the syndrome develops between the ages of 20 and 45 The extremes in Stern's series were 4 and 67 years.

Autonomic nervous system.—This relationship must be considered carefully since White and others have reported that ganglionectomy has a favorable effect on the condition Experience does not yet permit an ultimate evaluation of ganglionectomy for this particular syndrome

Avitaminosis.—Deficiency especially of vitamin B has been noted in persons with acrocyanosis, but much work must be done before a relationship can be seriously considered

PHYSIOLOGIC PATHOLOGY

Normal skin cooled to the point of cyanosis can be blanched somewhat if the part is elevated above the heart level, demonstrating lack of venous obstruction This also occurs in acrocyanosis Lewis and Landis demonstrated also that the white spot of Crocq disappears spontaneously and leaves no trace since it is due solely to the displacement of blood from the area by the pressure used Local trauma produces a red area within the cyanotic zone, which appears to demonstrate a breakdown in what is otherwise arteriolar obstruction The area of redness becomes greater than the original area of the trauma Furthermore, if the circulation to an acrocyanotic finger is occluded for five to 10 minutes, following release the reactive hyperemia extends 1–2 cm. proximal to the site of obstruction instead of being sharply limited to the obstructed point, as in the normal finger It is thought that these phenomena are due to a ready diffusion of the H (histamine-like) substance to the surrounding arterioles, producing dilatation.

These phenomena fit the hypothesis of Lewis and Landis that the mechanism of acrocyanosis is based on arteriolar obstruction If the hand is cyanosed and a small part of it is warmed, the area becomes bright red. Similarly, if a little histamine (1.3,000 solution) is injected, the local skin reddens and the temperature rises. In Raynaud's syndrome this response will not occur since the next larger set of arteries is involved and the phenomenon cannot develop until they have dilated. When testing for acrocyanosis, temperatures as low as 1–10 C. (34–50 F.) should not be used because in these patients, as in those with Raynaud's syndrome and normal individuals, the exposed parts become red owing to arteriolar injury, dilatation and retarded deoxygenation of the blood.

Until recently it was believed that no organic lesions were found with this syndrome. It is entirely reasonable, however, to suppose that repeated contraction of the arterioles continued over a period of years might well produce certain changes such as hypertrophy

of the medial layer. Stern reported having demonstrated this to be true He found that the medial coats of arterioles from 30 to 150 micrograms in diameter were thickened definitely or at least to the upper limits of normal He also found local edema and fibrosis of the skin, with dilatation and increase in the number of superficial capillaries Layani claimed that various blood disturbances were found with acrocyanosis, including prolonged coagulation time and lowered platelet count Stern checked these observations and many other factors and *concluded that no blood abnormality could* be demonstrated

The mechanism is probably a local sensitivity of the small vessels to cold or some vasomotor action producing increased arteriolar tone. Haxthausen and Lewis favored the theory that the vessels are especially susceptible to moderate cold, reacting in a diffuse manner rather than specifically to extreme cold injury They did not explain the source of the increased susceptibility Lewis *believed that response is localized to the arterioles of the skin be*cause the cyanosis is not relieved quickly by a nerve block, as would happen if the condition were on a vasomotor basis White, on the other hand, has suggested a purely vasomotor basis, claiming that the condition is relieved, as is Raynaud's syndrome, by complete preganglionic section. Obviously, this point must be clarified by further work

Signs and Symptoms

The word "acrocyanosis" was first used by Crocq, who described the syndrome as one in which the hands and feet become deep blue, especially in a cool environment, the blueness gradually fading out at the wrists and ankles, respectively The volar surfaces are moist, freely sweating, the dorsal surfaces are dry. Pressure produces a white spot which slowly disappears

Since Crocq's time, various workers have pointed out that his description requires amplification in several respects. The cyanosis

is not permanent, as Crocq thought, but disappears in all but the most extreme cases when the extremities are elevated or the environment is sufficiently warm. When normal skin is cooled it turns light blue owing to contraction of the arterioles and small arteries with resultant stasis and deoxygenation of the blood in the capillaries and the subcapillary venous plexus The deep blue of acrocyanosis appears to represent an extreme phase of this reaction Characteristically the color of the cyanosed skin is not uniform, there usually being scattered red areas (so-called cinnabar-red spots). The depth of color is usually greater in the dependent position A characteristic white spot noted by Crocq can be produced by local pressure It disappears spontaneously in a characteristic way, the color returning in one second to one minute and from the periphery only, rather than from below also, as in the normal skin.

Crocq did not mention edema, whereas in my experience local edema is fairly common. There may be merely a sensation of tightness, but in extreme instances edema may reach the stage where pitting is possible This is not seen in Raynaud's syndrome. Gangrene and ulceration do not occur in acrocyanosis except when frostbite or some other factor enters the picture, again in contrast to Raynaud's syndrome When traumatic or other lesions do occur, however, they easily become septic and heal with difficulty. Another feature of interest is the remarkably slight disability noted even in advanced cases Occasionally the skin follicles are abnormally prominent.

The sweating of the palms and soles when the patient is cool or even cold, but in the absence of emotional disturbances, is in marked contrast to Raynaud's syndrome and is almost specific for acrocyanosis. I have seen patients from whose hands sweat dropped regularly and frequently—five or more drops per minute This occurred in a cool environment in which gross sweating would ordinarily be absent. Kuno has shown that perspiration at low temperature occurs more on the palms and soles than elsewhere,

is increased by hyperemia and, failing to evaporate, collects on the surface When the circulation of the skin is shut off, perspiration becomes minimal and the skin becomes drier than in Raynaud's syndrome. Increased sweating keeps the stratum corneum moist and pliable and in patients who do little manual labor this layer tends to atrophy In day laborers, in contrast, one finds extremely thick, horny, dry skin. Mental stress will cause profuse sweating of the palms and soles In a cool environment the sweating causes chilling of the parts and the individual becomes more cyanotic In some cases cyanosis of the face and other parts is seen

Livedo reticularis (cutis marmorata) is not unusual with acrocyanosis In general, the symptoms and signs are more apparent in winter than in summer Even in the most extreme cases, the normally palpable arteries are patent, the circulatory interference apparently being due to spasm of the smaller vessels

Treatment

Treatment is not very satisfactory The patient and the part should be kept warm, either locally or by moving to a warm climate The patient should be as active physically as possible within reason Mental strain should be reduced to a minimum, and psychiatric care should be instituted when indicated Thyroid extract or thyroxin should be administered if the basal metabolic rate is low A high vitamin régime is usually given empirically If the syndrome is due to frostbite or trench foot time should be allowed for it to subside to minimal limits before it is evaluated This may take more than three years In the rare severe cases the possibility of a preganglionic resection may be considered

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CHAPTER XVIII Erythermalgia (Erythromelalgia)

RED, PAINFUL extremities have been observed for many years. Gray described a case in 1834 S. Weir Mitchell studied the disease in detail and described it under the term "erythromelalgia" The term "erythermalgia," suggested by Smith and Allen, more accurately describes the syndrome, in which the extremities are red, hot and painful There are other syndromes in which the extremities are red, painful and cold that should not be classified as erythermalgia Erythermalgia occurs in two forms (1) primary or idiopathic erythermalgia which, as the name implies, is not produced by or associated with any known agent, and (2) a large group, called secondary erythermalgia, which may occur in a number of conditions, although the mechanism is seldom clear I have seen it associated with hypertension, polycythemia vera, diabetes mellitus, gout and rheumatoid arthritis, and it has been reported with mercury, arsenic and thallium poisoning Information regarding the underlying pathology is striking for its absence

CLINICAL PICTURE

The condition usually occurs in men or women of middle age; it is rarely seen in younger people. The patient complains of a burning pain in the soles or palms Occasionally the discomfort is confined to one or two digits. Relief is usually obtained by removal

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Etiologic Classification of Sudden Arterial Occlusion (Modified)

I Embolism
  A Cardiac
    1 Auricular fibrillation, any cause
    2 Myocardial infarct with mural thrombosis
    3 Mitral and aortic valvulitis
      a) Bacterial, acute and subacute
    4 Failing heart from any cause
  B Arterial
    1 Mural thrombosis
      a) Aneurysm
      b) Arteriosclerosis
      c) Trauma
      d) Inflammation
  C Venous
    1 Through patent foramen ovale
II. Thrombosis
  A Inflammatory
    1 Thromboangiitis obliterans
    2 Periarteritis nodosa (polyarteritis nodosa—essential polyarteritis)
    3 Mycotic arteritis (severe infections)
  B Degenerative
    1 Arteriosclerosis—atherosclerosis
  C Traumatic
    1 Cervical rib, scalenus anticus, costoclavicular and hyperabduction syndromes
    2 External trauma
    3 Gunshot and stab wounds
  D Miscellaneous
    1 Infectious diseases
    2 Heart disease
    3 Blood dyscrasias
    4 Surgical procedures
    5 Idiopathic thrombophilia
    6 Trauma
III Ligation and severance

By far the commonest cause of arterial embolism is chronic auricular fibrillation with or without signs of congestive heart failure. The usual etiologic factor in young people is old rheumatic heart disease with auricular fibrillation and the development of thrombi on the mitral or aortic valve In middle age there is also a high incidence of arterial emboli from old rheumatic heart disease, but in addition there is an increasing incidence from mural thrombi secondary to coronary thrombosis with myocardial infarc-

CHAPTER XIX Acute Arterial Occlusion (Arterial Embolism; Acute Arterial Thrombosis)

ARTERIAL EMBOLISM is one of the most dreaded complications of cardiovascular disease Its occurrence is always associated with the possible death of tissue. Although minute emboli in certain areas may not produce significant disturbances, a large embolism may mean gangrene of an extremity. If the embolism is to the mesenteric arteries it may mean gangrene of a portion of the intestinal tract. If it is to the cerebral arteries, it may mean paralysis of any degree up to hemiplegia or it may mean death Pulmonary embolism is discussed in Chapter XX.

It is sometimes difficult to differentiate between the occurrence of an arterial embolism to a vessel of the extremity and a sudden occlusive process of the same vessel that is secondary to a local arteriosclerotic plaque with development of thrombosis or to an occlusion from thromboangiitis obliterans. Differentiation is especially difficult in the presence of generalized arteriosclerosis in an older person.

ETIOLOGY

Allen, Barker and Hines have suggested an etiologic classification of sudden arterial occlusion which appears to be helpful.

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- B. Arterial
  - 1 Mural thrombosis
    - a) Aneurysm
    - b) Arteriosclerosis
    - c) Trauma
    - d) Inflammation
- C. Venous
  - 1 Through patent foramen ovale

II Thrombosis
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  - 1 Thromboangiitis obliterans
  - 2 Periarteritis nodosa (polyarteritis nodosa—essential polyarteritis)
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- C Traumatic
  - 1 Cervical rib, scalenus anticus, costoclavicular and hyperabduction syndromes
  - 2 External trauma
  - 3 Gunshot and stab wounds
- D Miscellaneous
  - 1 Infectious diseases
  - 2. Heart disease
  - 3 Blood dyscrasias
  - 4 Surgical procedures
  - 5 Idiopathic thrombophlebitis
  - 6 Trauma

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tion. In the older age groups there is an increasing incidence of the last-mentioned type of lesion plus fibrillation secondary to degenerative changes without coronary occlusion at least of the major vessels

Thrombi occurring anywhere along the arterial tree may break loose and produce embolic phenomena distal to that point This often happens with arteriosclerotic aneurysms, especially those in the popliteal space, where movement of the leg tends to bend and stretch the aneurysmal sac more than elsewhere.

Sclerosis of the aorta with marked roughening of the intima and the development of local thrombi is a surprisingly rare source of emboli. Sudden arterial occlusion is rare in peripheral vascular diseases except arteriosclerosis obliterans and thromboangiitis obliterans. In these, it is usually a terminal episode of local narrowing of the lumen, with the final step thrombosis If the presence of these diseases is recognized the diagnosis is not difficult except when, in addition to the occlusive arterial disease, the patient's heart is fibrillating The differential diagnosis between an embolism and a sudden local occlusion may then be impossible clinically.

Signs and Symptoms

In about 50 per cent of patients, acute occlusion of an artery is characterized by sudden severe pain at the site of the occlusion, frequently extending distally. Either with or without pain, the patient frequently experiences marked numbness or tingling, and the extremity characteristically feels cold Loss of strength may not be noticeable at first but increases after a day or two. The extremity soon becomes pale, and in the following few days either returns to normal color or continues to be pale with increasing patchy, dusky cyanosis. Frequently the pulse returns to the level of the occlusion after having been absent for 10 or 12 in proximal to that site during the first few hours. This is especially likely to occur with an embolic phenomenon that has caused spasm of the arterial wall secondary to the shock of the original embolic episode.

Sudden occlusion must be differentiated from acute thrombophlebitis, this is not usually difficult. In thrombophlebitis the temperature of the involved extremity is likely to be increased, especially locally, and edema is often present. The extremity feels engorged and heavy. If thrombophlebitis is superficial, a cordlike vein usually is visible or palpable. This is all in contrast to acute arterial occlusion in which the extremity is usually pale, cool and, if anything, somewhat reduced in size. Occasionally acute thrombophlebitis produces occlusion of the associated artery by spasm. We have seen gangrene result from this

A late complication may be ischemic neuritis, due to degenerative changes in the nerves resulting from ischemia Gangrene occurs as a not infrequent end-result If, however, the occlusion has a more gradual onset, time is permitted for collateral circulation to become activated and the incidence of gangrene is somewhat reduced

Patients have been seen with fibrillating rheumatic hearts who have survived many emboli

We have one patient who has had 21 recognizable emboli to various extremities and the mesenteric, cerebral, pulmonary and renal arteries. Although this patient has been near death on several occasions, the emboli have not been large enough to produce permanent serious effects, but she is living with the Sword of Damocles over her head She had seven emboli within a month, the last one to the bifurcation of the brachial artery of the left arm, the effect of which cleared in four days Under continuous ambulatory treatment with Dicumarol she went 3½ years without an embolus then decided to discontinue this therapy Exactly 30 days later she had an aortic saddle embolus and nearly died She has been on anticoagulant (Dicumarol) therapy for the past two years, again free from emboli, although her heart continues to fibrillate

There are now more than 50 such patients in our series under study Embolization is being prevented by Dicumarol or Tromexan.

A tragic case is under my care. A young girl, who did not know that she had heart trouble, went to have the premarital Wassermann test

tion. In the older age groups there is an increasing incidence of the last-mentioned type of lesion plus fibrillation secondary to degenerative changes without coronary occlusion at least of the major vessels

Thrombi occurring anywhere along the arterial tree may break loose and produce embolic phenomena distal to that point. *This often happens with arteriosclerotic aneurysms, especially those in the popliteal space, where movement of the leg tends to bend* and stretch the aneurysmal sac more than elsewhere.

Sclerosis of the aorta with marked roughening of the intima and the development of local thrombi is a surprisingly rare source of emboli Sudden arterial occlusion is rare in peripheral vascular diseases except arteriosclerosis obliterans and thromboangiitis obliterans In these, it is usually a terminal episode of local narrowing of the lumen, with the final step thrombosis. If the presence of these diseases is recognized the diagnosis is not difficult except when, in addition to the occlusive arterial disease, *the patient's* heart is fibrillating The differential diagnosis between an embolism *and a sudden local occlusion may then be imposs*ible clinically

Signs and Symptoms

In about 50 per cent of patients, acute occlusion of an artery is characterized by sudden severe pain at the site of the occlusion, frequently extending distally Either with or without pain, the patient frequently experiences marked numbness or tingling, and *the extremity characteristically feels cold. Loss of strength* may not be noticeable at first but increases after a day or two. The extremity soon becomes pale, and in the following few days either returns to normal color or continues to be pale with increasing patchy, dusky cyanosis. Frequently the pulse returns to the level of the occlusion after having been absent for 10 or 12 in. proximal to that site during the first few hours This is especially likely to occur with an *embolic phenomenon that has caused spasm of the* arterial wall secondary to the shock of the original embolic episode.

major arteries of the extremities will develop gangrene. Some improvement in this figure by rational local therapy has been reported, but it is difficult to evaluate critically any of the reports on individual agents because the investigators have usually employed a number of forms of therapy simultaneously in a justifiable endeavor to save the extremity One must guard against a natural human fault, namely, the tendency to attribute therapeutic success to whichever agent one is particularly interested in

The following forms of treatment used in combination have proved most successful in our hands

1 The head of the bed is elevated so that the affected extremity is at least 6 in below the heart level. The limbs should never be elevated above the heart level.

2 Normal room temperature is maintained; it should never be above 90 F. (32 2 C.).

3 The use of tobacco is definitely interdicted.

4 Alcohol is given freely in the form of whisky or brandy, with 1 or 2 oz every three to four hours, depending on tolerance.

5 Papaverine hydrochloride, ½–1 gr (0 032–0 06 Gm) may be given intravenously or into the artery proximal to the occlusion. If the first or second injection does not achieve a definite vasodilating response, it is doubtful that further injections will be effective. Favorable reports have been published regarding the effect of papaverine administered orally, but for the most part the studies have not been well controlled

We have been studying the effect of papaverine given intra-arterially in the affected limb. The injection of 1 gr (0 06 Gm) directly into the femoral or brachial artery will frequently produce a striking increase in warmth and in some cases a conspicuous flush, even in an extremity which was cold and cyanotic. This response has occurred in extremities in which repeated lumbar sympathetic blocks had failed. If the response is good the injection *may be repeated every six hours*—or even more often—watching carefully to be certain that untoward effects from papaverine do

required by the State of New York. Her family physician listened to her heart and found that it was fibrillating. This had not previously been recognized The Wassermann reaction was negative. In a few days she had an embolic episode which resulted in complete right-sided hemiplegia with total aphasia, from which recovery has been very incomplete. The fibrillation continues There is a history of undiagnosed fever three months before which was probably atypical rheumatic fever. Five years later she has marked residual signs and plans for her marriage have long since been abandoned.

Emboli arising from the left side of the heart may travel to any portion of the major circulation, which includes that to the extremities and the cerebral vessels as well as the abdominal arteries. Emboli from the right side of the heart, or the venous circulation, can travel only into the pulmonary circuit unless there is a patent foramen ovale through which they can pass into the left side of the heart and thence into the major circulation Usually thrombi are forming in one or the other side of the circulation. However, in old, badly damaged, fibrillating hearts, thrombi are often formed simultaneously in both sides and may break off into the major or the minor circulation

Treatment

Formerly the treatment of acute arterial occlusion was devoted almost exclusively to the local problem The decision to attempt surgical removal of the embolus must be made promptly, since the passage of even a few hours may render potentially successful surgery useless. In general, surgery may be attempted with reasonable prospect of success if the embolus is at the bifurcation of the aorta or the femoral arteries and a well trained surgical and anticoagulant team is available and if surgery is done within 12 hours. For emboli peripheral to these vessels or in the upper extremities, conservative therapy produces at least equally good results.

If nothing but the simplest conservative treatment is carried out, approximately 50 per cent of patients with sudden occlusion of

on anticoagulant therapy. Massive hemorrhages, some of them fatal, have occurred in the deep tissues at the site of such injections. Anticoagulant therapy should therefore be deferred until sympathetic blocks are discontinued

Sympathectomy has been recommended, but the results are unpredictable unless a preliminary paravertebral block causes a striking increase in circulation, indicated by a rise in surface temperature and an improvement in the appearance of the limb There are a few enthusiastic exponents of sympathectomy despite failures

General sympathetic block *with tetraethyl ammonium chloride* and allied substances has been introduced and may be used The safe dose for TEA (Etamon) is 3–10 cc. intramuscularly every three to six hours Blood pressure must be watched carefully for precipitous drops which occasionally occur. Its effectiveness is still *to be evaluated Priscoline, 25 mg every three or four hours* by mouth or intra-arterially, is being widely used

10 As noted earlier, in the presence of massive embolus to the bifurcation of the aorta or the femoral artery, surgery should immediately be considered. If it is to be done, it should be done quickly as an *emergency procedure Surgery for the removal of* emboli is highly technical and should be undertaken only where there is available a trained team composed of a surgeon, an internist and an anesthetist who work together not only to remove the embolus successfully but to give the anticoagulant therapy necessary to prevent the recurrence of a thrombus at the site of the operation In general, the operation should be done within four hours, or at the longest 10 hours, after the embolic episode Gerald *H Pratt* has, however, performed an operation on one of my patients for removal of a thrombus from a saddle embolus more than 70 hours after the embolism occurred

The condition seemed almost hopeless, but Pratt was prevailed upon to operate, with results much better than could be anticipated Under local anesthesia a silver wire with a corkscrew end was introduced

not develop—excessive drowsiness, disorientation, and the like

Priscoline (15-25 mg.) intra-arterially in the affected limb every three to six hours has also proved helpful.

The technic for intra-arterial injection is simple for the femoral artery but more difficult for others, depending on their site and the degree of obesity of the patient

Papaverine (0 06 Gm) or Priscoline in solution is diluted in 5 cc distilled water A 5 cc. syringe with 2 in 20 gauge needle is used The artery is located by its pulsations, fixed between the second and third fingers of the left hand, and the needle is guided directly into it as one would do a venipuncture. Cutting down on the artery is almost never necessary. Entrance into the artery is recognized by a pulsating surge of bright red blood into the syringe The solution is then slowly injected into the artery, the needle withdrawn and firm pressure applied for two or three minutes The effects are noted in five to 10 minutes, gradually extending peripherally to the farthest possible point compatible with the available circulation

It is my belief that this is a highly effective measure and should be used more freely. The ultimate evaluation remains to be made.

6. The use of reflex heat by means of a heating pad applied to the abdomen or under the lumbosacral area has some value Heat above 96 F. and refrigeration should never be applied directly to the involved extremity or refrigeration used except for preamputation anesthesia Many limbs have been lost by the injudicious use of these agents.

7 The pressure-suction boot and intermittent venous occlusion apparatus have generally been abandoned

8. The oscillating bed (p. 145) appears to have more physiologic foundation than most apparatus and is widely used

9. Paravertebral anesthesia, used in an endeavor to increase the vasodilatation of the vessels of the extremity, has been widely advocated. It appears to be effective but must be repeated several times within two to three days if any response is to be maintained. Intra-arterial injection of papaverine may supersede this procedure.

Sympathetic blocks should not be undertaken if the patient is

is made, administration of anticoagulants should begin immediately, especially if surgery is not contemplated If surgery is being considered, it is wise to wait until after the operation before giving an anticoagulant Heparin should be injected at the site of the operation to prevent the development of secondary thrombi, and within several hours after termination of the operation larger amounts of heparin may be administered intravenously. There may be some loss of blood unless the vessels are firmly sutured, but this is seldom a serious complication and is definitely less serious than the development of thrombi at the operative site Heparin may be administered during the first few days postoperatively either by continuous intravenous or by intermittent injection technic (p. 424) Usually the second postoperative day Dicumarol may be given, beginning with 300 mg by mouth, or Tromexan, beginning with 1,500 mg by mouth.

If surgery is not contemplated, Dicumarol or Tromexan may be administered alone, without heparin, unless the condition seems acute and multiple emboli are being released, in which case the immediate effect of heparin is desirable

I have observed more than 50 patients with auricular fibrillation who have had from two to 21 recognized emboli In an attempt to interrupt the propagation of the original thrombus in the heart which was releasing the emboli, the patients have been placed on a prolonged anticoagulant régime In each, Dicumarol or Tromexan has been started under carefully controlled conditions in the hospital for one month, during which time the prothrombin rate has been kept between 30 and 50 seconds After the dosage has been stabilized the patients have been released to continue anticoagulant therapy on an ambulatory basis but to have the prothrombin level checked at least three times a week The desired level has been considered to be between 25 and 35 seconds

The series is growing, the longest period of observation being five years The incidence of emboli has been sharply reduced Nearly every embolus has occurred when the prothrombin time

through the femoral arteries and the thrombus extracted (Fig 88). The patient survived, with one good leg and loss of the other leg below the knee, which made it possible for him to continue his career as minister

Surgical removal of emboli from arteries smaller than the fem-

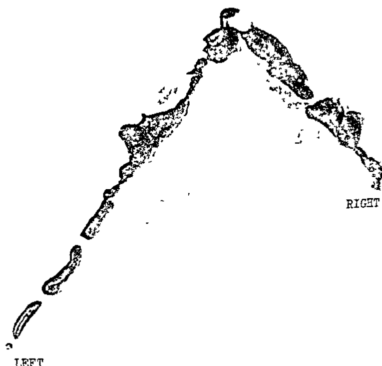


FIG 88 —Portions of thrombus removed from saddle embolus.

oral is generally less popular than it was a decade ago, the trend now being toward sympathetic blocks and anticoagulant therapy.

11. The use of anticoagulants in treatment of emboli has received prolonged study Anticoagulants should be given to prevent propagation of the embolus or the suddenly occlusive thrombus and also to treat the original source of the embolus, for example, a thrombus in the heart or elsewhere in the body. Once the diagnosis

Anticoagulant therapy should be administered to all patients who have had or are suffering from embolic phenomena, whatever their source, unless there are definite contraindications. It is probably wise to continue the therapy for at least three or four weeks after the last episode in order to encourage complete sealing of the original thrombus Specific directions for this treatment are given on pages 423 ff For more complete information regarding thromboembolic conditions and their treatment with anticoagulants, the reader is referred to the monograph by Marple and Wright

The local treatment for emboli to the kidneys, lungs, brain and other internal organs is largely expectant It is sometimes possible to operate successfully on the intestinal tract following embolism or thrombosis In general, the physician should concern himself primarily with the prevention of further episodes, anticoagulant therapy offers the major hope in this regard.

11 Refrigeration should not be used to save the extremity, but it may be used to reduce pain or toxic absorption once the decision to amputate the limb has been made

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has dropped below the optimal therapeutic level (25–35 seconds). The total period for all of these patients is now approximately 100 years. Several patients who discontinued anticoagulant therapy did have emboli within a month afterward. Final evaluation of this procedure has been difficult However, these patients had been having series of embolic episodes immediately preceding the institution of anticoagulant therapy and the process stopped with its inauguration. This represents a logical attempt to interrupt the fundamental process responsible for repeated emboli of this type.*

In May of 1942 we started to treat a series of patients with coronary thrombosis with myocardial infarction with Dicumarol By 1945 experience with 80 such patients suggested that this was a sound approach since it appeared that both the death and the complication rate was reduced. Nichols and Page, and Peters, Guyther and Brambel confirmed this observation. Following this, the Committee on Anticoagulants of the American Heart Association was established A case study of 1,031 patients with acute attacks was carried out. Approximately half of them received heparin or Dicumarol, or both The other half did not, but were otherwise treated in the same manner. Sixteen leading cardiologists and their hospital teams participated in this study The results have been published widely, but in summary The mortality rate has been reduced approximately one-third, from 23 to 15 per cent, and the rate from thromboembolic complications four-fifths, from 41 to 11 per cent Table 10 shows the incidence of complications in the first 800 cases.

TABLE 10—INCIDENCE OF POSTEMBOLIC COMPLICATIONS IN 800 CASES

	Cases per hundred	
	Controls	Under anticoagulant Therapy
Extension of original infarct	9 0	2 0
New infarcts	6 5	2 5
Pulmonary emboli	9 4	2 6
Cerebral emboli	3 4	0 7
Peripheral emboli	3 0	1 0
Venous thromboses	5 0	2 0

* The first preliminary report of this treatment for the condition was presented by the author before the Philadelphia College of Physicians in December, 1946.

Anticoagulant therapy should be administered to all patients who have had or are suffering from embolic phenomena, whatever their source, unless there are definite contraindications. It is probably wise to continue the therapy for at least three or four weeks after the last episode in order to encourage complete sealing of the original thrombus Specific directions for this treatment are given on pages 423 ff For more complete information regarding thromboembolic conditions and their treatment with anticoagulants, the reader is referred to the monograph by Marple and Wright

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CHAPTER XX. Thrombophlebitis; Phlebosclerosis; Obstruction of Vena Cava; Pulmonary Embolism

THROMBOPHLEBITIS

THROMBOPHLEBITIS INCLUDES a variety of diseases having different etiology, precipitating factors, gross pathology, course and prognosis. Because this has been insufficiently emphasized in the past, it is not surprising that conceptions of the processes involved and the treatments indicated have been chaotic and conflicting.

ETIOLOGY AND CLASSIFICATION

The classification presented here is from the Nomenclature of Diseases of the Blood and Lymph Vessels, prepared by the Committee on Nomenclature of the Section for the Study of the Peripheral Circulation of the American Heart Association It is at once apparent that thrombophlebitis is not a single syndrome but a many-headed hydra

DISEASES OF VEINS

Organic (Structural)

A. Obstructive
  1. Thrombophlebitis and venous thrombosis (phlebothrombosis)
    a) Primary
      (1) Thromboangitis obliterans
      (2) Recurrent or migrating (without arterial lesions)
      (3) Essential

- *b)* Secondary to
  - (1) Mechanical injury (contusion, laceration, surgery)
  - (2) Muscular effort or strain
  - (3) Chemical injury (sclerosing agents, drugs, solutions for diagnosis)
  - (4) Inflammatory or suppurative lesions—infectious diseases
    - *(a)* Tuberculosis, syphilis, actinomycosis
    - *(b)* Other bacteria (to be specified)
  - (5) Severe ischemia
  - (6) [illegible]
  - (7) [illegible]
  - (8) [illegible]
- 2 *Neoplastic invasion of vein*
- 3 Venous compression—with or without thrombosis or thrombophlebitis due to
  - *a)* Gravid uterus
  - *b)* Neoplasm
  - *c)* Aneurysm
  - *d)* Scar tissue
  - *e)* Scalenus syndrome
  - *f)* Fractures and dislocations
  - *g)* Increased intra-abdominal pressure (ascites, etc)
  - *h)* Extrinsic pressure (tight girdles, circular garters, poorly made trusses, etc)

B Nonobstructive

- 1 Varicose veins (aneurysm)
  - *a)* Primary—congenital incompetent valves
  - *b)* Secondary (to proximal obstructive lesions or pressure)
  - *c)* Secondary to phlebitic destruction of valves
  - *d)* Compensatory dilatation of collateral veins
- 2 Arteriovenous fistula
  - *a)* Congenital
  - *b)* Traumatic
  - *c)* Mycotic
  - *d)* Secondary to local disease
- 3. Aberrant position
- 4. Hypoplasia
- 5 Phlebectasia
- 6 Periphlebitis without thrombosis
- 7. Phlebosclerosis (not usually obstructive)
- 8. Rupture

The differences in etiology and mechanism are clearly demonstrated by this classification. In most instances several factors appear to play a part in the development of thrombophlebitis. For example: (1) by means of chemical irritation, trauma or dehydration, the intimal lining is damaged; (2) stasis is produced by

mechanical blockage such as pregnancy, abdominal binders or cardiocirculatory failure or varicosities, causing a strong tendency to thrombosis by a mechanism to be described later; (3) organisms of a variable or unknown type invade the thrombus through the blood or lymph streams

Ochsner and DeBakey have made the following differentiation between thrombophlebitis and phlebothrombosis

> The clotting in thrombophlebitis is the result of injury to the vascular endothelium from mechanical trauma, bacterial invasion or chemical injury, whereas in phlebothrombosis the intravascular thrombus formation is due to venous stasis and to alterations in the cellular and fluid constituents of the blood that increase the clotting tendency The prognostic significance of this differentiation lies in the fact that in thrombophlebitis the clot is usually firmly adherent to the vein wall and is, therefore, less likely to become detached and result in embolism On the other hand, in phlebothrombosis the coagulum is loosely attached to the vessel and is, therefore, likely to cause embolism

I have not been able to classify many cases so clearly into either of these groups Although in some patients the process at the time of onset is of one or the other type, after several days both processes are nearly always active. A thrombus need be adherent only a very short time before the intima is damaged and destroyed. On this or any other basis, no one is able to state definitely which patient will have emboli and which patient may die of emboli. Emboli seldom represent entire clots which come away from the vessel walls cleanly Instead they are apt to be bits of thrombus broken off from newly formed, extending portions of the red tail, especially as it reaches the next venous branch where the blood current exerts suction and torsion on the fragile mass It appears, therefore, unwise to base the prognosis on this system of differentiation. In fact, to give a prognosis in any case of active thrombophlebitis is hazardous—especially to the reputation of a physician prone to this form of mental gambling

The question of causative organisms remains as it was 10 years

- *b)* Secondary to
  - (1) Mechanical injury (contusion, laceration, surgery)
  - (2) Muscular effort or strain
  - (3) [illegible]
  - (4) [illegible]
  - (5) Severe ischemia
  - (6) Chronic disease of vein wall (varices, phlebosclerosis) (Late complications—varicose or postphlebitic ulcers)
  - (7) Blood dyscrasias (polycythemia vera, leukemia, pernicious anemia)
  - (8) Epidermophytosis (?)

2 Neoplastic invasion of vein

3 Venous compression—with or without thrombosis or thrombophlebitis due to
- *a)* Gravid uterus
- *b)* Neoplasm
- *c)* Aneurysm
- *d)* Scar tissue
- *e)* Scalenus syndrome
- *f)* Fractures and dislocations
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4 Hypoplasia

5 Phlebectasia

6 Periphlebitis without thrombosis

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has studied a substance which he has called factor V and which he believes is converted into an active factor VI during coagulation.

Other factors have been described by various workers but need further clarification before introduction into a work of this kind

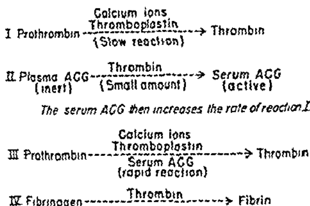


FIG. 90—Modern theory of mechanism of blood coagulation

Calcium, long considered indispensable to the production of a clot, is now not considered an absolute necessity from the theoretical point of view, although it probably has an important part in most clinical thromboses

The lipoprotein thromboplastin is present in nearly all tissues of the body but is especially concentrated in the brain, lung and placental tissues *It is essential to the completion of the process of thrombosis*

The final reaction is a conversion of fibrinogen by enzymatic action of thrombin Polymerization of fibrinogen units results in transformation to fibrin

The roles of heparin and other possible antithrombins in keeping the blood liquid by balancing against the clotting components are significant, but details regarding their action are lacking

Mellanby has shown that heparin is an antithrombin and not, as Howell believed, an anti-prothrombin. That is, it does not pre-

ago. No work has conclusively demonstrated that a single form of bacteria, fungus or virus is responsible for any one of the syndromes falling under the general classification of thrombophlebitis (the exception being the rare suppurative case with direct extension into the vein). This is surprising because the picture is so often typical of an infectious process, with swelling, redness, local heat, tenderness, pain, malaise, fever, tachycardia and increased sedimentation rate and white blood cell count. Dunham and I exhaustively cultured a number of sections taken from actively inflamed veins without obtaining consistent results. We obtained virus-like growths from sections from seven of 18 patients but were unable to keep them alive through serial passages and cannot state definitely that they are related to the disease, although the possibility must be considered. Study of these virus-like growths was interrupted by the war, further work might prove profitable.

PATHOGENESIS

The pathogenesis of thrombosis is extremely complicated, with many factors being involved and several steps progressing simultaneously in the blood. The classic theory of Morawitz (1905) is represented by the two equations in Figure 89. This was accepted

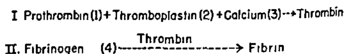


FIG. 89 —Classic theory of blood coagulation.

as a working hypothesis for 40 years until Quick, Owren and Seegers all reported the demonstration of additional factors. The factor which has been studied most completely is a globulin and has been named by Seegers the "accelerator globulin" (ACG). It greatly increases the rate of conversion from prothrombin to thrombin but, as seen in Figure 90, the mechanism is not clear. Owren

has studied a substance which he has called factor V and which he believes is converted into an active factor VI during coagulation.

Other factors have been described by various workers but need further clarification before introduction into a work of this kind.

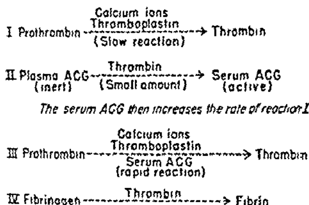


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vent the conversion of prothrombin to thrombin, but inactivates the latter enzyme after it has been formed. The inactivation depends on the presence of neutral salts, for dialyzed plasma *does* clot readily when thrombin and heparin, which ordinarily would not cause clotting, are added Heparin is present only in minute amounts in circulating blood and is probably not solely responsible for the maintenance of the fluidity of the blood in the living body. Jorpes has submitted evidence that heparin is present in, and may be produced by, the "mast cells" of Ehrlich, which are metachromatic staining cells with toluidine blue (Fig 91) and are found along the walls of blood vessels in many areas of the body. The full function of these cells and of heparin as it is found in the blood is not completely understood, but it probably tends to keep the blood fluid

It may be that the blood does not clot intravascularly simply because no thromboplastin is available to convert prothrombin to thrombin

For some years our laboratories, in collaboration with workers from the Chemistry Department, School of Electrical Engineering of Cornell University at Ithaca, have been studying the electric charges of different components of the blood and their possible role in the clotting mechanism Like charges are mutually repulsive, as they decrease, the repulsion may be reduced. Details regarding these and many other unanswered but basic problems of blood clotting are summarized in the Twelfth Annual George E Brown Memorial Lecture of the American Heart Association which I delivered in June, 1951

The foregoing hypotheses have been reviewed to show the trend of current thinking. They are being constantly revised on the basis of new evidence.

As the changes leading up to the production of fibrin take place, other mechanisms must come into play to produce a thrombus. In the living body a number of factors tend to protect the circulating blood against undesirable coagulation. Experiments by





FIG 91 —Mast cells, heparinocytes, around capillaries in subcutaneous tissue of the rat. These cells are concentrated storehouses of heparin and probably supply heparin to the blood Vital staining, × 700 (From Jorpes, J E *Heparin in the Treatment of Thrombosis* [2d ed , New York Oxford University Press, 1946], reproduced by courtesy of the author and publisher)

Glénard and by Baumgarten have shown that, under favorable conditions, blood between two ligatures applied to a vein may be kept stagnant without clotting if the internal lining of the vessel is unaltered and intact

Friedlander advanced the theory that some roughness of the intimal lining, perhaps secondary to injury, or the tiny nodules, described by Dietrich, that follow infection, is usually necessary to provide an anchoring buoy to which a thrombus is affixed when the circulation is disturbed, especially with a tendency to stagnation. Virchow considered a thrombus identical to an extravascular clot Zahn demonstrated the process of thrombosis Following an injury to the vessel wall, white cells and platelets collect at the site of injury and form a white "head" of the thrombus which is fixed to the wall The sticky insoluble fibrin plays an important part in this process, and all blood elements become involved The blood clot forms and is fixed at one end to the white "head," and the red "tail" of the clot usually begins by waving free at the other end In small veins the white head is often large in proportion to the rest of the clot, whereas in large veins the head may be almost invisible, the red tail making up most of the thrombus The complex interplay of all of the factors described, plus many others, including the relationships of glucose and the electrolytes, cannot be elaborated here Many of the links in this presentation must rest on reasonable hypotheses rather than established evidence

Many other factors have important roles in this process, of which the following deserve brief mention (1) Stasis of the blood with associated blood sludging (2) Platelet adhesiveness due to fibrin and the action of hydrophilic colloids on the surfaces (3) Malignancy, especially of the pancreas and liver, which is important in the production of intractable thrombophlebitis (4) Familial thrombosing tendencies We have studied one family with eight members in whom serious thromboembolic conditions have devel-

oped. Four died of these conditions. The mechanism is unknown (5) Idiopathic recurrent thrombosing tendencies Some patients continue to have recurrent episodes for many years, yet the abnormal changes in the blood may not be detectable (6) ACTH and cortisone apparently encourage the tendency to thrombosis.

Two conditions which produce temporary agglomeration of the blood and which may be confused with thrombosis but in which no true thrombosing mechanism is present are cryoglobulinemia and the syndrome of cold agglutinins

The movement of the blood through the veins depends on many factors, among them the sucking power of the regular pulmonary respirations which draws the venous blood toward the chest The venous valves prevent the blood from slipping back when intrapulmonary pressure increases. The skeletal musculature also acts by pressure on the vessel walls to force the blood along centrally Here again the venous valves assure a one-way process Two factors of slight, if any, importance are the pressure from the arterial side, vis a tergo, and the sucking power of the right atrium

The venous valves are damaged by trauma and infection and are common sites of thrombosis. The thrombus usually forms rapidly, and organization may begin in 24–48 hours. Propagation of a thrombus may, however, continue for days or intermittently for weeks. Involution proceeds during the following weeks partly by fibroplastic organization and partly by liquefaction Eventually, there is usually some return of function of the vein, but it is apt to be incomplete, especially since, as Edwards and others have pointed out, the valves rarely escape destruction

The foregoing description is of thrombosis as it occurs with intimal changes in thrombophlebitis It should not be forgotten that all layers of the vein wall are usually involved by the inflammatory process Indeed, Homans has shown that there is usually obstruction of the perivenous lymphatic channels during the acute stage In some cases the inflammatory reaction is practically con-

fined to the adventitia and outer layers without the production of thrombosis—thus, periphlebitis.

PATHOLOGIC PHYSIOLOGY

The pathologic physiology resulting from thrombophlebitis is due to interference with the return blood flow to the heart in the involved section of the venous tree This may not be important if only small branches are involved, because a great abundance of venous collateral vessels drains most of the tissues of the body. It should be realized that thrombophlebitis is often a multiple disease and that evidence of involvement in new areas must constantly be sought.

When large trunks are involved, serious secondary effects are frequently noted. If, for example, the iliofemoral or axillary vein is involved and obstructed by a thrombus that extends a considerable distance, the distal venous pressure at heart level may be quadrupled In the instance of the iliofemoral vein, when the patient stands the venous pressure may approximate the arterial diastolic pressure This inevitably causes intense congestion of venules and capillaries and subsequent transudation with edema

Homans has held that obstruction of the perivenous lymphatics is the major factor in the formation of this edema. I am inclined to agree with Barker that, especially in the early stages, most of the edema is probably due to capillary congestion, with a serious disturbance of the normal downward gradient of intracapillary pressure preventing the usual reabsorption of tissue and intracellular fluids by the capillaries The fact that ligation of the large venous trunk does not lead to edema is not adequate proof of Homans' theory, because thrombophlebitis most frequently inactivates an extensive portion of the involved vein by thrombosis, reflex spasm or both, thus usually blocking the return flow through collateral vessels It is probable that persistent chronic edema is in part due to blockage of the perivenous lymphatics, which may continue to be a factor long after the venous balance has been re-

stored toward normal by means of canalization and collateral activation

The obstructive process results in dilatation of the collateral veins They often overdilate, producing huge varices from the excessive burden thrown on their relatively weak valves and walls A vicious cycle is set up, since the valves are overstretched, become insufficient, produce additional reverse pressure on the venous walls and increased stagnation as they fail to hold the blood It is especially serious when the important saphenous valve at the femoral vein is insufficient, for then the entire venous pressure of the femoral-vena cava system reverses on the weak saphenous veins Valvular insufficiency commonly follows destruction of the valve leaflets by the process of thrombophlebitis

The basic phenomena are described at some length because the clinical symptoms and signs arise from them and because rational therapy should be considered in the light of its effect on them rather than on the more obvious manifestations.

SIGNS, SYMPTOMS AND COURSE

The signs and symptoms associated with the syndromes of thrombophlebitis vary widely with the type, location and extent of the lesion. Every possible combination cannot be described in detail, because the variations are almost countless. After accidental and surgical trauma and delivery the physician is on the watch for thrombophlebitis. He must not forget that thrombophlebitis may develop insidiously without a known precipitating factor and even without signs or symptoms preceding a fatal pulmonary embolism.

Pain.—The patient generally notices pain at the site of venous involvement. It may be slight, as with involvement of a small segment of an unimportant superficial vein, or moderately or extremely severe when large venous trunks are involved. It is sometimes described as a local sense of soreness. It may be referred, as in several patients with iliofemoral venous involvement, to the back, in the lumbosacral area. In some patients the back pain is extremely

severe, even agonizing, to the point where opiates are relatively ineffectual. It is not generally known, but this syndrome must sometimes be differentiated from an abdominal or psoas abscess and acute osteomyelitis of the spine.

In patients with migratory phlebitis the same type of local pain may involve various venous branches throughout the body. When a patient with thrombophlebitis develops pain elsewhere than the original site, a spread of the disease must be the first consideration.

I saw a patient who was treated with heparin for thrombophlebitis of the deep veins of the left leg for five days Ten days later, when she complained of pain in the right groin, the obvious implications were ignored She was told that she just had swollen glands and was allowed to be ambulatory without treatment, whereupon serious iliofemoral phlebitis developed and she became desperately ill.

Multiple lesions are commonly missed on routine autopsy examinations because studies of the veins, even in good hospitals, are unhappily very incomplete, even in patients who have died of primary or secondary effects of thrombophlebitis.

Any branch may be involved, although a thrombus does not necessarily occur at the site of each painful area. It appears in these cases that the lesions are essentially periphlebitic, involving the outer layers and producing a pain without thrombus and edema, in contrast to the more common episodes representing thrombophlebitis in which the thrombus and edema are the principal features and pain is minimal. In some patients the pains of periphlebitis are of extraordinary severity. Many times the two conditions are combined One other type of pain—general malaise—is frequently conspicuous. Contrary to the theories of Meyer, the pains of phlebitis should not be confused with those of rheumatism and "growing pains" Pain in the calf produced by forced dorsiflexion of the foot is sometimes suggestive of thrombophlebitis in the deep veins of the calf. It is known as Homans' sign. It is not infallible and may be confused with injury to the soleus

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muscle and inflammatory reactions in the muscles and nerves of the calf

Tenderness.—Associated with the local pain is tenderness, which in general extends along the course of the involved veins The tenderness is most diffuse when deep veins are involved, and in areas where the veins may be pressed on directly it is acute. These areas include the inguinal region, Scarpa's triangle, Hunter's canal, the popliteal space and the area directly at the middle of the calf.

Cramps.—A form of pain not often mentioned is that produced by severe muscular cramps which occur rather frequently with deep vessel phlebitis. These cramps may be extremely severe and very serious because it may be virtually impossible for the patient to lie still during an attack and the cramp may, by exerting distorting pressure on the vein, release an embolus. Cramps are especially apt to occur in the calf muscles, although they may affect any set of muscles in the body.

Color changes —Superficial thrombophlebitis is almost always accompanied by local redness of the skin directly over the area of inflammation and often extending as a red streak over the course of the vein Occasionally there is a diffuse area of redness resembling erysipelas. Several such patches may be seen in different portions or branches of the same venous tree. With migratory thrombophlebitis widely scattered patches of this type appear far from the primary site As the acuteness of the local process subsides the patches gradually turn a purplish brown and then a dull brown as they fade Some residual pigmentation may remain indefinitely.

A dusky cyanosis of the part distal to the occlusion of a large vein may be present early and may persist for a long period.

Color change that has serious significance is seen on rare occasions. The periphery of an extremity suddenly becomes pale bluish or blanched owing to spastic occlusion of an artery which rests against the acutely inflamed vein. This may be so serious as to

result in massive gangrene, as in the woman reported by Grégoire (cited by Homans) in whom exploration confirmed the suspected state of affairs. Figure 92 shows another example of this phenomenon, with resultant gangrene of the toes of the left foot of a woman, 40. In the presence of acute thrombophlebitis which had produced pulmonary emboli the arteries became pulseless and remained so for four days; after intra-arterial papaverine and reflex *heat therapy* the dorsalis pulse returned Although gangrene had



FIG 92—Gangrene resulting from arterial spasm secondary to thrombophlebitis (*Courtesy of Dr Theodore S Heineken, from Medichrome Series MM—Vascular Diseases, by I S Wright and W T Foley*)

already set in, the total tissue loss was not serious Pallor may also be seen in cases of milk leg, due to blockage of the iliofemoral veins and lymphatics resulting in pale edema

Local swelling—Accompanying the redness already described is usually a mild degree of swelling A lump or, more frequently, a cordlike mass is palpable along the course of the vein This type of swelling is not necessarily present and often cannot be felt when deep veins are involved.

Edema—Congestion of the entire venous and capillary bed distal to the site of blockage, in varying degrees, inevitably follows

thrombosis. There may be prompt adjustment without the development of gross edema, especially if the thrombosed vein is small and if adequate collateral venous return is available, as in the foot and calf. The opposite extremes are seen with blockage of larger veins, especially the femoral-iliac, resulting in phlegmasia alba dolens or milk leg. The edema is, as previously explained, due to obstruction with increased retrograde pressure in the venules, capillaries and lymphatics which disturbs the normal downward pressure gradient as the blood progresses from the arteries to the veins and hence interferes with the reabsorption of tissue fluids by the vessels. Gross edema has been present in approximately 50 per cent of our patients.

Fever —Fever may or may not be present. In three patients with seemingly identical degrees of thrombophlebitic involvement, one may have fever of 103–105 F (39–41 C) with chills, the second may have low grade fever of 100–101 F. (38–38.5 C.) and, less commonly, the third may have practically no fever

Tachycardia —This is common even when fever is not present. If persistent, it must be considered evidence of continued activity of the disease.

Sedimentation rate.—The sedimentation rate is unpredictable. In some patients it falls more than 100 mm. per hour (Westergren), whereas in others, whose veins appear to be more severely involved, the rate is well within normal limits (less than 16 mm per hour). There does appear to be some rough parallel between fever and the sedimentation rate. A normal rate has no significance. When high, it gives some clue to the rate and degree of recovery and serves as a guide to the degree of activity permissible to the patient. As long as the rate is elevated, any considerable activity appears ill-advised Contrary to early reports of some workers, Dicumarol therapy does not elevate the sedimentation rate. As patients recover from the disease, the sedimentation rate returns to normal while they are on Dicumarol therapy.

Blood count —The blood count also may or may not be affected

by thrombophlebitis. The white cell count may rise to 40,000 or more, with a high polymorphonuclear count and many young forms and toxic granulations Severe anemias may develop, with red cell count under 3,000,000 and hemoglobin content less than 40 per cent of normal In contrast, one patient had severe migratory phlebitis for more than nine months without abnormal changes in the blood count or sedimentation rate.

To re-emphasize, thrombophlebitis may occur in any vein of the body and symptoms will vary accordingly Thus, manifestations of liver, kidney, mesenteric, pulmonary and cerebral phlebitis are not uncommon but are frequently unrecognized

COMPLICATIONS AND SEQUELAE

The commonest and most dreaded complication of acute thrombophlebitis is pulmonary embolism Large emboli which cause sudden death or pulmonary signs and symptoms, including sharp pain, the coughing up of bright red blood and the development of signs of a patch of pneumonia, are usually recognized Observations, both of living patients by serial x-ray studies and at the autopsy table, show that more than half of pulmonary emboli are missed entirely or wrongly diagnosed This is particularly true of so-called postoperative pneumonias This situation could be measurably improved if greater attention were paid to all chest symptoms and signs occurring during postoperative periods and the puerperium and especially during attacks of active phlebitis.

Serious warning should be registered against the practice of conducting routine physical examinations of the chests of patients suspected of having or known to have thrombophlebitis, especially if there has been a suspicion of embolism *Forcing the patient to breathe deeply may, by producing negative pressure, suck off a portion of the tail of the clot with disastrous results* Rough manipulation or palpation of an involved extremity may also be extremely dangerous. Examinations of these patients require extreme gentleness, care and skill More frequent x-ray studies in doubtful

cases would help, they should be made with portable x-ray apparatus because unnecessary moving of these patients is risky.

Many fatal emboli occur without clinical evidence of phlebitis. Zilliacus has reported 114 such cases from Sweden (see Table 15, p. 420). Emboli are released in one of several ways (1) A por-



FIG 93 *(above)* —Cross section of tail of thrombus lying free in a vein Although thrombus is free at this point, the vein wall shows signs of inflammation This type is dangerous and the source of most pulmonary emboli

FIG 94 *(below)* —Remarkable example of propagation of a thrombus to length of 36 in This was removed whole from veins of leg by suction (Courtesy of Dr Gerald H Pratt)

tion of the tail of a fresh thrombus may break loose due to some increase in rate of flow or a twist of the vein, as in one of my patients with the thrombotic tendency typical of leukemia who had a pulmonary embolism after manipulation by a cult practitioner (2) The thrombus may extend from the vein in which it develops

into the lumen of the large venous trunk into which the vein drains If the current is strong enough to break off a piece of the tail, in a fraction of a minute we may have an embolus. Increased suction, as that produced by deep breathing, may seriously accentuate this risk. (3) Occasionally, because of very slow organization of the thrombus and in suppurative thrombophlebitis, a friable portion breaks loose spontaneously to become an embolus.

Barker cited a large series of patients with postoperative iliofemoral thrombophlebitis in whom fatal pulmonary embolism occurred in only 5 per cent, in half of these within four days. In one-half, the site of origin was an unrecognized fresh thrombus from the opposite vein. The incidence of embolism in recurrent thrombophlebitis was, in his series, approximately 12 per cent, and of fatal embolism, 7 per cent. In 300 cases we have studied from this point of view, pulmonary embolism was recognized in 26 patients (8 6 per cent), of whom six died. There were also 11 emboli to other parts of the body. Further discussion of pulmonary embolism will be found at the end of this chapter

Death from emboli which lodge in the chambers of the heart should also be mentioned. We have seen a number of these at autopsy The largest was 22 cm long and was coiled up in the right auricle.

Postphlebitic syndrome.—The frequency of recurrence of thrombophlebitis is not generally appreciated Over a period of 10 years, recurrences are seen in an average of 25–40 per cent of patients For accuracy it would be well to discontinue the use of the term "cured" and substitute "arrested" As with tuberculosis, in most patients who survive the first attack the condition is arrested and they do not have a recurrence. The risk is great enough, however, to justify planning of postphlebitic care on the basis of the dictum, "Once a phlebitic, always a potential phlebitic." This may be discouraging to some patients, but it will make them cautious and thereby reduce recurrences, as in arrested tuberculosis

The important and frequently disabling chronic after-effects of

thrombophlebitis include varicose veins of all degrees, chronic edema, varicose and other postphlebitic ulcers and chronic eczema, pigmentation, induration and other skin changes around the ankles

Mention should be made of the pains which persistently recur in the previously involved veins, especially with weather changes and on prolonged standing. They are not necessarily accompanied by reactivation of the disease. They may occur at lengthening in-



FIG 95—Thrombus of left common iliac vein large enough to produce a fatal embolus. (By courtesy of Dr John G Kidd)

tervals and with diminished intensity for some years after an acute episode.

The syndrome of postphlebitic neurosis has been described by Allen and Brown. It is seen most often in nervous women who have been in bed for a prolonged course of treatment and who have been overimpressed with the probability of permanent disability or pulmonary embolism. It is common, and not surprising, in patients who have had multiple attacks and who live in fear that each pain represents the first signs of a new attack. The prin-

cipal complaints are of excessive weakness and rather nebulous shifting pains in many areas of the body not confined to previously involved veins

MEDICAL TREATMENT (EXCEPT ANTICOAGULANTS)

A sound consideration of the treatment of thrombophlebitis must start with the dual premise (1) that thrombophlebitis is not a single disease but, in reality, represents a group of syndromes produced by a variety of etiologic factors, and (2) that the location of the thrombophlebitis may indicate need for wide differences in the therapeutic approach

The first step is thorough study to determine the cause and mechanism responsible for the disease in the individual patient. For example, thrombophlebitis secondary to polycythemia vera requires specific treatment of the underlying disease, quite a different procedure from that used for thrombophlebitis secondary to chemical injury, such as a faulty injection of Pentothal sodium, and from that needed for thrombophlebitis associated with early thromboangiitis obliterans *Fatal emboli may even arise from chemically produced thrombophlebitis following treatment for varicose veins.* Such a case occurred on one of our services. If a sharply localized thrombophlebitic process in the lower extremity is releasing multiple pulmonary emboli, ligation may be a logical procedure *Failure to consider the possibility of involvement in several segments of the venous tree (some of the sites may be symptomless) and to treat the patient on that basis constitutes lack of comprehension of the fundamental process or dereliction of therapeutic responsibility on the part of the physician.*

Ten years ago, those recommending conservative therapy were not in a very strong position Today, the situation has been radically changed by the introduction of anticoagulants The availability of various anticoagulants, discussed in detail later, has not, however, obviated the need for meticulous observation of certain fundamental principles of conservative therapy.

In addition to the care of any underlying disease, the treatment may take several forms, to be undertaken concurrently when indicated. The local lesion is considered first, it being necessary to reduce pain and swelling. Swelling may be relatively slight and localized or may involve one or more entire extremities. The second consideration is management of other thrombophlebitic lesions, which may or may not be recognized at the time, but which may be the source of serious or deadly emboli. The third includes the treatment of pulmonary and other embolic phenomena The fourth aspect confronting the physician is the necessity for care and detailed interest in his patient after the active process has subsided and the immediate danger passes This care must be continued for one to several years and sometimes for life Too frequently the doctor dismisses the patient after the acute phase is over without giving adequate instructions and maintaining proper follow-up care

An attempt will be made here to present in a practical and concise form the therapeutic methods which have been established as useful by clinical and experimental observations on approximately 2,000 patients seen in civilian and Army hospitals during the past 20 years. Of these, approximately 1,300 were treated with anticoagulants. There is still controversy regarding some of the technics to be discussed, and the ideas expressed are not to be considered final; indeed, it is hoped that new concepts will be forthcoming

Elevation.—An involved extremity should be elevated approximately 6 in. above the level of the heart. This is especially indicated in the presence of edema. The purpose is to facilitate drainage of static lymph and venous fluid from the extremity. The measure adds greatly to the patient's comfort. Elevation is best accomplished by raising the foot of the bed 12–15 in. on blocks. The use of pillows alone too frequently results in elevation of the knee above the foot and therefore interference with proper drainage distal to the knee In the presence of occlusive arterial disease it is unwise to elevate the extremity. The use of an oscillating bed

will help to reduce the edema safely. Otherwise keep the extremity in a horizontal position.

Rest.—Although it is important to keep the patient active as a preventive postoperative measure in order to discourage the production of clots and the development of thrombophlebitis, once thrombophlebitis has been recognized undue activity should be prevented This is contrary to the view of some European workers, but on numerous occasions we have seen patients who had been placed on a régime of walking 20 to 60 blocks daily during phases of an acute process and in whom mild and relatively innocuous thrombophlebitis of a small vein distal to the knee rapidly extended up into the iliac vein and even the inferior vena cava In view of anticoagulant therapy, except for a few superficial, chronic, low grade instances of involvement of varicose veins, the routine of bandaging the leg and walking is dangerous and obsolete

Avoidance of deep breathing and straining—At all times during the active phase of thrombophlebitis, and especially if there has been any suspicion or evidence of embolic phenomena, it is extremely important that the patient avoid deep breathing, coughing and straining in any way Too frequently when the patient complains of pain in the chest and coughs up a little blood, the house staff and attending physician undertake a thorough examination of the chest, including auscultation during deep breathing and coughing, in an endeavor to determine the site of the infarct Since the diagnosis is in most such cases almost certain, the localization must be considered a matter of academic interest only If it is essential to make a differential diagnosis or know the site of the infarct, an x-ray taken by carefully slipping a cassette under the patient will serve adequately

The reason for this warning is clear The movements of respiration are among the most important factors concerned with the return of blood to the heart Deep breathing introduces negative phases of pressure which tend to free loosely attached thrombi, or tails of thrombi, with serious consequences I have been present at

In addition to the care of any underlying disease, the treatment may take several forms, to be undertaken concurrently when indicated. The local lesion is considered first, it being necessary to reduce pain and swelling Swelling may be relatively slight and localized or may involve one or more entire extremities. The second consideration is management of other thrombophlebitic lesions, which may or may not be recognized at the time, but which may be the source of serious or deadly emboli. The third includes the treatment of pulmonary and other embolic phenomena The fourth aspect confronting the physician is the necessity for care and detailed interest in his patient after the active process has subsided and the immediate danger passes. This care must be continued for one to several years and sometimes for life. Too frequently the doctor dismisses the patient after the acute phase is over without giving adequate instructions and maintaining proper follow-up care.

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Nerve blocks do not cause the thrombus to disappear suddenly. The risk of embolus remains, but pain and edema are sometimes remarkably diminished The hot pack method has the advantage of application for as many days as is deemed advisable.

Quinine sulfate.—Night cramps are not uncommon with thrombophlebitis or varicose veins For such cramps quinine sulfate is sometimes helpful in doses of 0 2 Gm. at bedtime or with a similar dose at suppertime

Fluids—It is important that the patient have not less than 3–4 qt of fluids a day in order to avoid dehydration, which increases the thrombosing tendency Provided the sodium chloride intake is not increased, water per se seldom contributes to the edema, especially if the extremity is elevated, since the edema is not on a metabolic, renal or cardiac basis.

Antifungus therapy—Dermatophytosis must be actively combated One of the most satisfactory methods is soaks of potassium permanganate 1 5,000 solution for 30 minutes every other day Whitfield's ointment, half-strength, and various new antifungicides such as Sopronol (Wyeth) or Timofax (Burroughs Wellcome) may be tried, always with care not to overtreat and thereby cause a highly irritated reaction in the area

ANTICOAGULANT THERAPY

The dramatic story of how hemorrhagic spoiled sweet-clover disease in cattle led Link and his co-workers to the discovery, isolation and synthesis of Dicumarol and allied derivatives is medical history Clinical investigations of the value of this substance were reported in 1941 by Meyer, Bingham and Pohle, by Butt, Allen and Bohlman and by Prandoni and Wright All three groups of workers found that *in man*, as in lower animals, Dicumarol prolonged the prothrombin time and delayed coagulation of the blood There was a lag of 24–72 hours before the action in the blood was measurable It was found that the material was effective when given orally and that transfusions of fresh whole blood would

several autopsies on patients who died during or soon after unwise physical examination

The patient should be warned against straining at defecation, and one of the physician's functions is to see that laxatives and enemas are used to prevent the need for such straining

Heat —The local use of either an ice bag or a hot water bag has largely been superseded by the application of moist hot packs to the full length of an involved extremity This results in remarkable relaxation of both venous and arterial trees, comparable to that produced by lumbar ganglionic procaine block. The technic follows.

The extremity is covered with cold cream to protect the skin from maceration A light blanket or one or two large turkish towels are dipped in hot water, wrung out and wrapped loosely around the entire extremity Four to eight hot water bags are then laid along the leg and wrapped in a large loose rubber blanket Electric heating pads may be used, but only if waterproofed This is continued for 20 hours out of 24, the skin being allowed to aerate for four hours After four to eight days, if improvement warrants, the length of time of application is reduced gradually Usually after 10–14 days the packs may be discontinued

One thing that increases the patient's discomfort is the weight of the heavy hot water bags on the extremity At our suggestion Margaret Braley devised light, plastic, sealed bottles which contain a chemical solution that retains either heat or cold for five or six hours after immersion in hot or cold water for 15–20 minutes They are light, pliable, made to fit the extremity and do not leak A plastic case 27 in. long with pockets within which such containers can be inserted, and wide enough to wrap around an extremity, has also been devised and is about to be made available to the medical profession *

One to four or more paravertebral sympathetic nerve blocks may be performed to break the reflex arc of spasm during the first few days, using 2 per cent procaine solution They may be performed once or twice daily for three or more days. The hot packs will prolong and enhance the effectiveness of such blocks.

* Made available by Comfort Pack, Old Greenwich, Conn

for an insufficient time with Dicumarol. This record is especially noteworthy because 379 of the patients had already demonstrated thrombotic tendencies, having had thrombosis or embolism, and 438 had an abdominal hysterectomy, an operation for which the statistical risk of thrombosis is high (See Table 11.)

The effect of Dicumarol therapy on thrombophlebitis has also been clearly shown by Barker Among 897 controls with thrombo-

TABLE 11 —DANGERS OF POSTOPERATIVE AND OBSTETRIC THROMBOPHLEBITIS *

	Cases of Thrombosis	Pulmonary Embolism Cases	%	Fatal Pul. Embolism Cases	% of Cases of Thromb
Surgical cases					
Schneidegg *et al*	1,500	746	48 1	298	19 2
Barker *et al.*	1,665	897	53.8	343	20 6
Obstetric cases					
Holzmann *et al*	749	119	15 8	26	3 47
Hellsten	420	150	35 8	20	4 76

* Courtesy of Dr J. Erik Jorpes
Note how closely the figures for the two surgical series coincide and how widely they vary from the figures for the obstetric series, which also coincide

phlebitis who did not receive anticoagulant therapy, 95 (10 6 per cent) had subsequent episodes and 51 (5.7 per cent) died of fatal pulmonary embolism In contrast, of 138 patients with thrombophlebitis to whom Dicumarol had been administered, 4 (2.9 per cent) had subsequent episodes and none had fatal pulmonary emboli. These figures are sound evidence that when Dicumarol is administered an established thrombus will almost certainly not detach itself and become an embolus, nor will it tend to propagate

Tables 12–15 give figures compiled by Jorpes, Bauer and Zilliacus of Sweden on results with anticoagulants These and other figures indicate that there is little difference in the results of anticoagulant therapy whether heparin or Dicumarol is used but that anticoagulant therapy definitely improves the prognosis.

There have been some cases reported, and I have seen a few, in which emboli occurred during Dicumarol therapy In almost every instance I have investigated, the emboli occurred (1) in the first 24–36 hours, before the full effect of Dicumarol had been

usually promptly restore the prothrombin time. When 60–72 mg of vitamin K is given in single or multiple doses it shortens the lengthened prothrombin time which follows the administration of Dicumarol. Prandoni and I first reported that in man, as in lower animals, hemorrhagic manifestations may follow excessive doses of Dicumarol and that, therefore, the drug perforce must be administered with care and respect in order to avoid serious hemorrhagic manifestations.

Dicumarol impairs or prevents coagulation of the blood by reducing the amount of prothrombin in the circulating blood It is fairly certain, though not proved, that the site of prothrombin synthesis is in the liver and that Dicumarol inhibits prothrombin synthesis, thus interfering with the production of the classic expression prothrombin + calcium + thromboplastin = thrombin; fibrinogen + thrombin = fibrin.

It is now well established that the effective anticoagulants, including Dicumarol, heparin and the more recently studied ones, Tromexan, Phenylindanedione, BL5 (Cumopyran) and Paritol, will help prevent venous thrombosis, thrombophlebitis and emboli More extensive experience has been gained with Dicumarol and heparin than with the others, so that experience will be more liberally cited.

When Dicumarol has been administered after surgery in the pelvic area and other regions in which thrombophlebitis is known to be a common complication, there has been a striking reduction in the incidence of thrombophlebitis Once thrombophlebitis is established, Dicumarol conspicuously reduces the number of pulmonary emboli and leads to their abolition in most instances. Marple and I have reviewed this entire subject in detail in a recent monograph

Barker and his co-workers from Mayo Clinic reported the use of Dicumarol in 1,000 cases for the purpose of preventing postoperative venous thrombosis. There was only one death from pulmonary embolism and this occurred in a patient who was treated

for an insufficient time with Dicumarol. This record is especially noteworthy because 379 of the patients had already demonstrated thrombotic tendencies, having had thrombosis or embolism, and 438 had an abdominal hysterectomy, an operation for which the statistical risk of thrombosis is high. (See Table 11)

The effect of Dicumarol therapy on thrombophlebitis has also been clearly shown by Barker Among 897 controls with thrombophlebitis who did not receive anticoagulant therapy, 95 (10 6 per cent) had subsequent episodes and 51 (5.7 per cent) died of fatal pulmonary embolism In contrast, of 138 patients with thrombophlebitis to whom Dicumarol had been administered, 4 (2 9 per cent) had subsequent episodes and none had fatal pulmonary emboli These figures are sound evidence that when Dicumarol is administered an established thrombus will almost certainly not detach itself and become an embolus, nor will it tend to propagate.

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TABLE 12—COMPLICATIONS OF THROMBOSIS WITH AND WITHOUT ANTICOAGULANT THERAPY (ZILLIACUS)

		Thrombosis	Pulmonary Embolism	Spread to Other Leg
No specific treatment		214	60 (20*)	66
Heparin	342			
Heparin and Dicumarol	103	576	8 (1*)	9
Dicumarol	131			

* Deaths

TABLE 13—COMPARISON OF RESULTS IN THROMBOTIC CASES TREATED CONVENTIONALLY AND WITH ANTICOAGULANTS, MAINLY HEPARIN, 1940-44*

	Without Anticoagulants		With Anticoagulants	
	Cases	Deaths	Cases	Deaths
Med. Clinic A	16	9	22	0
Surg Clinic A	71	17		
Surg Clinic B	41	5	26	0
Surg Clinic C			74	0
Surg Clinic D	33	11	31	1
	161	42	153	1

* Collected from five Swedish clinics Courtesy of Dr J Erik Jorpes

TABLE 14—RESULTS WITH AND WITHOUT ANTICOAGULANT THERAPY (BAUER, ZILLIACUS)

		Thrombosis or Pulmonary Infarct		Deaths	%
Conservative therapy		543		88	16
Heparin	769	900	3	4	0 45
Dicumarol	131		1		

TABLE 15—SUDDEN PULMONARY EMBOLISM WITHOUT OTHER THROMBOTIC SYMPTOMS (ZILLIACUS)

	No	Deaths
First attack fatal	114	114
First attack not fatal		
Conservative treatment	65	21 (30%)
Heparin or heparin-Dicumarol	103	0

achieved, (2) during therapy when the prothrombin time had been allowed to drop to the original normal level or below, or (3) after Dicumarol therapy had been discontinued and the prothrombin time had returned to normal or below. It is advisable, when discontinuing Dicumarol, to decrease the dosage gradually to obviate the tendency to overcompensation on the part of the

liver Heparin should also be discontinued gradually unless hemorrhagic complications force its abrupt cessation

In the Mayo series of 1,000 treated patients only 30 (3.7 per cent) developed minor bleeding and 25 (2.5 per cent) major bleeding The only case of fatal bleeding occurred in a patient who had carcinoma of the third portion of the duodenum which required extensive resection with some trauma to the superior mesenteric vein, it is doubtful that Dicumarol played a role.

Among 2,000 persons in my series, none had fatal pulmonary emboli during Dicumarol therapy, two died of hemorrhage probably related to Dicumarol One bled from a rectal cancer, one, with severe hypertension, died of cerebral hemorrhage. Desperately ill with thrombosing disease, both were given anticoagulants as a calculated risk

TABLE 16.—RESULTS IN FIRST 400 CASES ON ANTICOAGULANT THERAPY (TREATED OR SUPERVISED BY WRIGHT)

Cases without embolism before treatment	277
Embolism developed during treatment (early)	3
Cases with embolism	123
Embolism during adequate anticoagulant therapy	2
Embolism after cessation of therapy	1
Deaths from embolism	0

Any unexplained difficulty in controlling the prothrombin level with Dicumarol, especially in the presence of migratory thrombophlebitis, should cause one to consider the possibility of a malignancy, especially one involving the liver, pancreas, or both. We encountered four such cases before 1946 (Table 17) Since then we have seen numerous additional patients whose thrombophlebitis was resistant to anticoagulant therapy and who later were proved to have cancer Although the pancreas and liver have been the commonest sites of the cancer, other organs, including the uterus, stomach, lungs and breasts, also have been involved.

In 1941 we described rather extensive hemorrhages produced by Dicumarol, but at that time the dosage for man was not well understood and the tests for controlling the dosage were not satis-

TABLE 17—COMPLICATIONS IN FIRST 400 CASES ON ANTICOAGULANT THERAPY (WRIGHT)

Inability to control thrombophlebitis		5
Causes — 1 Malignancy of liver	2	
pancreas	1	
intestine	1	
2 Phlebitis migrans	1	
Deaths from underlying disease	4	
Hemorrhagic manifestations		25
Purpura of skin and mucous membranes	21	
(In last 200 cases, after therapy was standardized	2)	
Frank hematuria	4	
(In last 200 cases, after therapy was standardized	2)	
Deaths from anticoagulant therapy		0

factory Furthermore, we were dealing with seriously undernourished individuals. Since then I have seen several cases with hemorrhagic manifestations in which the drug had not been administered with sufficient caution or the tests for prothrombin levels were not satisfactorily performed by the laboratory, thus giving the clinician a false sense of security. Such situations must be most carefully guarded against if Dicumarol is to be used

Use of anticoagulants for the most part has been associated with a prompt subsidence of the symptoms of thrombophlebitis. Autopsy examinations of patients who have died of other causes after a week or more of anticoagulant therapy have usually revealed sealing of the proximal ends of the thrombi wherever they were found. In a few patients thrombophlebitis has continued throughout treatment or has lighted up after the anticoagulant has been discontinued. These have been patients with so-called idiopathic migratory thrombophlebitis—a much less tractable and more serious syndrome than the usual postoperative, post-traumatic and postinfectious types. On the other hand, in a number of such patients the disease was apparently arrested. It is felt that the prognosis with anticoagulants is somewhat better than that with any other therapy. A second, resistant group, includes those with malignancy.

INDICATIONS FOR CAUTION IN USE OF ANTICOAGULANTS

1 Prothrombin deficiency (hypoprothrombinemia)
   a) Vitamin K deficiency
   b) Severe hepatic disease
2 Blood dyscrasias with disturbances in normal mechanisms for hemostasis
3 Renal disease, especially with hematuria
4 Marked hypertension
5 Ulcerations or open wounds with bleeding tendencies
6 Subacute bacterial endocarditis
7 Vitamin C deficiency
8 Pregnancy, especially with toxemia
9 Certain surgical operations
   a) Recent operations on brain and spinal cord
   b) Procedures leaving raw surfaces
   c) Procedures with tube drainage
   d) In presence of obstructive jaundice, biliary fistula or severe liver damage

Inadequate laboratory reports and lack of meticulous interest on the part of the physician are serious contraindications to the use of anticoagulants

For a discussion of the use of anticoagulants in the treatment of coronory thrombosis and its thromboembolic complications, the reader is referred to Chapter XIX on Acute Arterial Occlusion

Technic of administration of anticoagulants —(1) The prothrombin time is determined by the Quick or Link-Shapiro technic before the first dose is given Normal readings are 12–13 seconds by the Quick method and 13–17 seconds by the Link-Shapiro method (2) If the prothrombin time is normal or lower, 300 mg of *Dicumarol* is administered orally in one dose If emboli have occurred, heparin may be started immediately and continued until the Dicumarol effect is manifested (This is discussed in detail later) (3) Each day the prothrombin time is determined and reported to the physician in charge of the case before the Dicumarol dosage for that day is decided on. (4) Dicumarol is administered in doses of 200 mg daily until the prothrombin time is 30 seconds, and in doses of 100–200 mg. (depending on the patient's sensitivity to the drug) daily when the prothrombin time is between 30 and 35 seconds on the ascending portion of the curve (5) When the prothrombin time reaches 35 seconds, Dicumarol is discontinued until the prothrombin time drops below 30 seconds, after which it is given again cautiously in daily doses of 100–200 mg (The foregoing prothrombin time values were determined by the Link-Shapiro method, for which

see the Appendix) Frequently the time rises for several days after Dicumarol is discontinued and then returns toward normal

(6) If the prothrombin time reaches 60 or 70 seconds, hemorrhagic manifestations may occur, and one must be alert to the possibility. At a level of 60–65 seconds 64–72 mg of vitamin K should be given parenterally and repeated in four hours. Since 1942, hemorrhagic manifestations have been confined to very rare patients with purpuric spots, minor oozing from the gums and some red blood cells in the urine. More severe hemorrhagic manifestations may be checked by one or two transfusions of 300–500 cc of whole fresh blood (may be citrated) (7) The objective is to keep the prothrombin level between 30 and 50 seconds, especially during the first two or three weeks The dosage is then tapered off slowly, permitting the time to drop below 30 seconds, followed by a gradual return to normal Dicumarol has been continued in most of our cases for 20–30 days after the last episode of thrombosis or embolism

When numerous embolic phenomena have already occurred it is sometimes advisable to give *heparin* during the first 24–48 hours until the effect of the first dose of Dicumarol is established. Numerous discussions have been presented regarding the administration of heparin Continuous drip still appears to be the theoretical method of choice, although it is difficult to regulate and hard on the patient. In practice, few hospital staffs can continue the régime required for many days without some break in the technic. The clotting time must be checked every two hours day and night by the Lee-White method. The optimal time should be between 25 and 45 minutes to insure effectiveness without danger of hemorrhage.

Intermittent parenteral injections of heparin cause wide fluctuations in clotting time This method, giving 50–75 mg.* intravenously every three hours, is widely used in Sweden and has been favorably reported on by Jorpes, Bauer, Zilliacus and others The clotting time rises rapidly to 60–70 minutes and falls toward normal before the next dose is given. This seems risky and unphysiologic, but the Swedish workers have demonstrated that, practically, it is sound For ten years we have used this method extensively, with satisfactory results and without complications. The use of a vehicle causing slow absorption would be helpful, but to date those proposed have been disappointing Pitkin's men-

* The international standard used in the United States is 160 per cent as strong that used in Sweden, hence our dosage is apparently lower than the 75–125 recommended by the Swedish workers

stratum, including the recent modifications, causes wide fluctuations and difficulty in control and its use has been so painful that many patients prefer continuous infusion. It may also cause nausea. Depo-heparin (Upjohn) is less painful and somewhat more satisfactory to use but is still unpredictable. We use the following dose schedule. 200–300 mg. for the first dose and 200 mg on an average of every 12 hours if the clotting time is not in excess of 20 minutes just before the next dose If it is in excess of this, the dose should be delayed accordingly.

Sublingual administration of heparin has failed completely to produce any change in the clotting in tests run in our laboratory

Tromexan.—Tromexan, which is also a coumarin derivative closely related to Dicumarol, on the average acts more quickly and on discontinuation ceases to act more quickly than Dicumarol. We have come to use it almost entirely in place of Dicumarol, but others still prefer the latter drug With Tromexan, the first dose is 1,500 mg (1,800 mg if the patient is large) The second day the prothrombin time is usually prolonged If it is not above 35 seconds, the patient is given 300 mg three times (total 900 mg) Thereafter the usual dosage is 300 mg two or three times a day, depending on the prothrombin time. Divided dosage is much the most satisfactory with Tromexan When the prothrombin time is more than 35 seconds, the omission of one or two doses will almost invariably lead to a drop to therapeutic or normal levels within 24–36 hours. We have almost eliminated the need for vitamin K or transfusions by the careful handling of Tromexan on our service Some workers find this drug more difficult to control than Dicumarol

Phenylindanedione.—This too has been used as an anticoagulant It is not a coumarin, but it does reduce the prothrombin activity and thus prolongs the prothrombin time Blaustein has found the most satisfactory initial dose to range from 150 to 200 mg; further doses are adjusted according to the prothrombin time tests. The action of PID, as it is called, resembles that of Tromexan more than of Dicumarol, although some patients are

very resistant to it, and this represents a real disadvantage. Another disadvantage is that overaction cannot be counteracted by vitamin K It has no known advantages over Tromexan

4-Hydroxycoumarin No 63 (BL5; Cumopyran).—Used experimentally, this drug acts at about the rate of Dicumarol, but its action is much more prolonged so that doses need be administered only at two to five day intervals. The average dose is 125–150 mg and should be regulated by the prothrombin time tests. Overaction is counteracted rather inadequately by water-soluble vitamin K preparations but vitamin K_1 oxide in doses of 200–500 mg. will restore the prothrombin time to normal. This substance appears to require more study before final evaluation and recommendation for general clinical use

Paritol.—This preparation, a synthetic polysulfuric acid ester of polyanhydromannuranic acid, is similar to heparin in chemical structure and action but is less expensive to produce. It is being subjected to clinical investigation in our laboratory and elsewhere but is not quite ready for clinical use at this time

A lipid thromboplastin inhibitor described by Overman from our laboratory and by Tocantins acts on factor V but is still in the animal experimental stage

dl–Alpha tocopherol.—Careful studies in our laboratory and elsewhere have failed to confirm the claims that derivatives of dl-alpha tocopherol with or without calcium act as anticoagulant substances when administered to man or are significantly effective in the prevention or treatment of thromboembolic conditions.

Because of considerable variation in strength of the various thromboplastins used for tests of prothrombin time, it seems advisable to check each group of determinations daily against those in one or two healthy and supposedly normal individuals Pooled lyophilized plasma (Lyovac) has been used as the standard control, against dilute plasma 1·8 The control figure using Lyovac by this technic runs from 36 to 42 seconds

Workers differ as to the preferred manner of reporting on prothrombin activity. It can be reported either in seconds of time or in percentage of activity. To use the percentage of activity method, a dilution curve such as those devised by Quick, Shapiro or Barker is necessary To produce a reliable curve many determinations must be made from a number of samples; it is not advisable to use curves based on a small group of determinations

Inasmuch as a curve may contain a certain element of error, the percentage method naturally suffers from this disadvantage. It has also been found that many laboratories do not use any of the aforementioned curves, merely making a rapid calculation as follows control 14 seconds, patient 28 seconds, therefore the patient has 50 per cent prothrombin activity This result bears no relation to the curves of Quick, Shapiro or Barker and illustrates the confusion produced by this additional step. There seems to be no real advantage in taking the extra step of transposition of time to percentage, and confusion and error arise from it Therefore I recommend that the report submitted to the clinician be in seconds and that this always be accompanied by the control figure for that day Except for research studies or in unusual cases, we have not found the dilute (12 5 per cent) prothrombin times essential for clinical purposes

The use of anticoagulants requires well trained teams of workers and laboratories prepared to provide meticulous service. Unless the laboratory's technic for determination of the prothrombin time is properly standardized and can be depended on, use of Dicumarol or Tromexan should not be undertaken Only in favorable circumstances is home therapy with anticoagulants recommended When it is undertaken, provision must be made for frequent determination of the prothrombin level by reliable laboratory technicians Otherwise, it is certain that both the patient and the physician are in a hazardous position and may regret having used the drug For the convenience of a laboratory which may wish to

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adopt a proved method, the technic for determining plasma prothrombin is given in the Appendix.

TREATMENT OF THE POSTPHLEBITIC SYNDROME

A few words should be included about the care of the postphlebitic syndrome When the patient is ready to get up and about, as judged by subsidence of the local and general symptoms and normal pulse and sedimentation rates for 10 days or more, he should be briefed on what to expect in the future If the phlebitis involved his legs, he must understand that prolonged standing or even sitting may produce edema and that prolonged pitting edema may develop into a hard, nonpitting and permanent form due to the development of fibroblasts and lymphoblasts in the edema fluid He must, therefore, take steps to prevent this, and thus decrease the tendency to varicose veins and chronic leg ulcers

The most useful steps are. (1) the wearing of firm, knee-length elastic stockings at all times when he is up, especially for the first year or two, (2) elevation of the foot of his bed so that each night there is ample opportunity for the edema fluid to drain out of the leg, and (3) movement of the extremity under water, as in quiet swimming, which will quickly reduce the edema In other words, every effort should be made to prevent the edema from becoming static or fixed until the compensating venous and lymphatic circulation is able to assume the burden of its removal.

The patient should be warned that he may have pains in his legs and elsewhere, probably in the veins, for months or even years. Some patients become psychoneurotic regarding such pains, since they fear that each episode represents the beginning of a recurrence of the thrombophlebitis. Since most of the pains are of no consequence and, although annoying, last only a short time, the following arbitrary rule often helps these patients. "If the pain lasts less than one hour, forget it. If it lasts more than an hour, lie down with your feet elevated. If, after doing that, severe pain continues for a total of three hours, call your doctor." This rul

has considerably diminished apprehension and unnecessary calls on the physician

It is generally wise to advise the patient to avoid exercise which requires sudden twists, turns and stops, such as tennis, squash, handball and horseback riding, for at least a year. Numerous recurrences have resulted from such exercises Many patients discover that swimming, especially ocean swimming, is beneficial in reducing edema and discomfort Walking with elastic stockings on is a good form of exercise.

The patient must always guard against the development of dermatophytosis, and any evidence of it must be treated according to previously mentioned technics

Reassurance and use of the foregoing technics will conspicuously reduce the five, 10 and 15 year incidence of postphlebitic varicose veins, edema and psychoneurosis Unless the physician recognizes the need for this type of follow-up care, his treatment of the thrombophlebitic patient will be incomplete

SURGICAL MANAGEMENT

With the improvement in anticoagulant therapy the need for surgical intervention in thrombophlebitis is becoming rarer. In some circumstances, however, surgery is still indicated: (1) lack of facilities for anticoagulant therapy, and (2) hemorrhagic blood dyscrasias in the patient

For a complete discussion of the surgical technics of ligation and modifications of this procedure, the reader is referred to Pratt's monograph, *Surgical Treatment of Vascular Diseases.*

It must be pointed out that the only sound objective of a ligation is the prevention of an embolism arising in the ligated vein from reaching the heart or lungs. Ligation does not (1) affect the inflammatory process of the thrombophlebitis in the vein ligated, (2) affect thrombophlebitis in other veins, (3) prevent pulmonary emboli from other veins, or (4) guarantee that emboli will not arise from the proximal side of the site of ligation The last is

especially apt to occur when the vein wall is inflamed. I have seen two fatal cases of emboli from this site and Pratt has reported two such cases

Most expert surgeons in this field have abandoned prophylactic ligations except in unusual circumstances, and the ligation procedures are being generally superseded by anticoagulant therapy.

The wide variety of problems encountered in cases of thrombophlebitis is illustrated by the following vignettes.

Case 1.—This represents perhaps the most frequently encountered group A man, 21, convalescing normally from an appendectomy, noted on the ninth postoperative day a sense of stiffness in the right calf. Homans' sign was present. There were tenderness on deep palpation of the right calf and slight edema of the right foot and ankle. Two days later there was *pain in the groin* The *diagnosis* was thrombophlebitis involving the deep veins. Dicumarol therapy was initiated and the leg was elevated and placed in warm moist packs Within three days the condition began to subside, and he was discharged from the hospital two weeks later Recovery was uneventful

Case 2—A physician aged 36 was operated on for appendicitis On the eleventh postoperative day he was seized with excruciating pain in the lumbosacral region. He was unable to lie quietly despite ½ gr. of morphine The severe pain continued for several days, during which diagnoses of psoas abscess, acute osteomyelitis of the spine and pelvic peritonitis were considered After three days the right leg became swollen and a typical picture of femoral thrombophlebitis developed Because of the lumbar pain it was assumed that the pelvic and other iliac veins had probably been primarily involved. At that time anticoagulant therapy was not available. The course was stormy, with temperature 103 F. (39 4 C) or higher each day At the end of six weeks the condition in the right leg subsided, but the left leg promptly showed the same type of involvement All told, the fever continued for 3½ months, and it was five months before the patient was able to [illegible] careful, [illegible] or 3½ [illegible] lebitic pains with a drop in barometric pressure. He has now gone 14 years without a recurrence.

Case 3—A man of 34 had what seemed to be low grade thrombo-

phlebitis of a vein in the dorsum of the right foot It appeared to have been initiated by his habit of tying his shoe laces very tightly, thus traumatizing the vein walls against the bones of the arch of the foot Several such cases have been seen Anticoagulant therapy was not then available The condition progressed gradually to involve the veins of the entire leg, then it spread to the opposite leg, both arms, the scalp, trunk, lungs, mesentery and coronary veins After eight months of illness heparin became available and was given for 16 days During therapy the temperature remained normal, but within 10 days after cessation it rose again At the end of the tenth month the patient's son had mumps The patient contracted the disease, with bilateral parotitis and unilateral orchitis He was desperately ill. The temperature rose to 106 5 F (41 4 C), then dropped by crisis With the clearing up of the mumps, the phlebitis disappeared. The explanation for this was never completely clear, hypotheses included hyerpyrexia or some type of virus response He had a brief recurrence two years later, but otherwise has been well for 12 years

Case 4—A woman aged 48 developed severe milk leg bilaterally following the birth of her second child 23 years before this hospitalization There were large varicose veins of both legs and bilateral edema Over a period of years a most unusual network of enormous varicose veins had developed over the entire abdominal wall Three days before hospitalization these abdominal veins suddenly became inflamed and she had severe thrombophlebitis, with cordlike thromboses palpable throughout the network. She was treated with Dicumarol, hot moist packs and rest in bed The episode completely subsided, and she was discharged from the hospital in four weeks

Case 5—In a woman of 54, thrombophlebitis developed in the saphenous veins of the calf of the left leg She was treated conservatively at home without anticoagulants The episode subsided Two weeks later, on the advice of a local physician, she was hospitalized and had a bilateral saphenous ligation The third postoperative day an embolism developed in the lower lobe of the right lung Following this the temperature subsided and she returned home, but two weeks later she had a second pulmonary embolism and became acutely ill Acute thrombophlebitis with extreme tenderness involving all visible veins together with extensive edema then developed in the right leg and she was hospitalized for Dicumarol therapy The third day after admission she sank into a mixed stuporous and delirious state from which she never regained consciousness The prothrombin level was very difficult to



Fig. 96.—Legend on facing page.

control, ranging within 24 hours between 20 and 90 seconds on well regulated dosage. This led to the suspicion that she might have a carcinoma of the liver, but her condition did not allow a careful, complete clinical and x-ray survey. She died three weeks later.

Autopsy showed marked bilateral thromboses of the femoral and iliac veins extending to and including the lower portion of the inferior vena cava. The primary disease was carcinoma of the rectum with metastases to the liver which had replaced about three fourths of the hepatic tissue There were also metastases and old infarcts throughout the lungs.

Case 6—A middle-aged obese laborer whose occupation required standing for long periods developed an acute pain in the upper part of the abdomen After considerable discussion an exploratory laparotomy was done, but nothing significant was found The physical examination gave negative results, although obesity prevented a detailed study of his lungs He died five days later Autopsy revealed extraordinarily large thrombi involving both pulmonary arteries and some lodged in the chambers of the heart (Fig 96). This case illustrates the possibility of a fatal thromboembolic syndrome without clinical evidence in the lower extremities, although the casts of the thrombi indicated that they must have come from the large veins of the legs

There is an important group of patients who have had chronic constant or recurrent thrombophlebitis for many years. In the past, the therapy was never satisfactory Today encouraging results may be obtained, as illustrated by the following cases selected from numerous similar ones.

Case 7—Eight years before hospitalization a worker in a dress shop suffered an injury to the anterior surface of the left tibial area by striking it against a shelf The skin was not broken, but thrombophlebitis developed in the local area She continued to work The low grade process did not subside and in the intervening years had been continuously active It had been difficult for her to continue working because of pain, but she had persisted except for one month's rest At the

←Fig 96—Autopsy specimens from patient with fatal thromboembolic syndrome *A*, folded embolus, 45 cm long, that blocked both pulmonary arteries *B*, another large embolus coiled in right ventricle. *C*, emboli shown in *A* and *B* and others from same patient Rule is 15 cm long (Courtesy of Dr John G Kidd)



FIG. 96 —Legend on facing page

swelling of the legs. Exhaustive blood and serologic studies were unrevealing Cultures for virus, bacteria and fungi gave negative results Epidemiologic studies did not clarify the picture

Veins were sectioned and studied by several pathologists Their studies disclosed subacute phlebitis limited to the vasa vasorum (some found intimal thickening). The majority of the vasa vasorum were filled with leukocytic thrombi many of which contained eosinophils as well as polymorphonuclear leukocytes In a few of the vessels these inflammatory cells invaded the walls of the vasa vasorum and in a few, perivascular cuffing was noted. Some swelling was noted in vessels not containing the thrombi

The surgeons all noted increased fibrosis surrounding the affected veins, *but in no case was a thrombus found in the large veins* Prolonged bed rest resulted in remissions ACTH had no effect on the course At the time Dr Pearson reported this to me three girls had had recurrences after a month of freedom from symptoms

Although periphlebitis without thrombosis is not extremely rare, I have no knowledge of a similar epidemic

PHLEBOSCLEROSIS—VENOFIBROSIS

Phlebosclerosis is often seen in the form of calcified lesions of the veins They may be in the form of phleboliths, which are most commonly seen on x-ray examination in the pelvis and along the course of the veins of the leg Many elderly patients, especially those with chronic varicose veins, have marked calcification extending along the veins for a considerable distance. The lesions are usually associated with old thrombi in those veins which have calcified It is unusual for calcification to occur in the medial coat

Venofibrosis has been described as occurring in relatively young persons, between 18 and 45 There are loss of endothelium and hydrolyzation of the surface of the lumen of the vein. Fibrosis takes place, with marked hyperplasia of the fibrous tissue in the media The veins, usually of small order, are not dilated The in-

time of hospitalization there were definite redness, tenderness and [illegible]

The leg was elevated and hot moist packs were applied Dicumarol treatment was given for one month and the activity in the veins subsided The thromboses became less palpable, although they could still be felt The local heat and tenderness disappeared At the end of a month she was discharged from the hospital with the process apparently inactive

During a follow-up period of nine months the patient remained free from more than mild discomfort She returned to work and apparently made an uneventful recovery An attempt was made to prevent a relapse by decreasing the periods of standing at her work and by having her wear elastic stockings Two years later a recurrence was responding to the same therapy

Case 8 —A woman had 11 attacks of acute thrombophlebitis within two years The series of episodes was terminated by one month of anticoagulant and hot pack therapy In a 12 month follow-up she had no further recurrence

Migratory thrombophlebitis may be an incurable and tragic disease, and no one can predict which first attack may be the onset of the syndrome

Case 9.—A nurse struck the side of the left calf against a hospital bed in 1937 A minor bruise was followed by a small area of thrombosis. The condition became more severe, with involvement of various other veins of both legs and, successively, the mesenteric, splenic, pulmonary, coronary, abdominal wall and cerebral veins She became psychotic and was confined to a hospital for mental diseases 10 years later. The phlebitic process continued to progress despite all forms of therapy

Phlebodynia (Epidemic)

Dr John S Pearson has given me permission to include a description of a very unusual, if not unique, experience he has encountered at St. Mary's Hospital, Huntington, West Virginia. In the fall and winter of 1950–51, 19 student nurses developed a symptom complex consisting of severe pain along the course of the superficial saphenous vein in Hunter's canal and with slight

swelling of the legs Exhaustive blood and serologic studies were unrevealing Cultures for virus, bacteria and fungi gave negative results. Epidemiologic studies did not clarify the picture

Veins were sectioned and studied by several pathologists. Their studies disclosed subacute phlebitis limited to the vasa vasorum (some found intimal thickening). The majority of the vasa vasorum were filled with leukocytic thrombi many of which contained eosinophils as well as polymorphonuclear leukocytes In a few of the vessels these inflammatory cells invaded the walls of the vasa vasorum and in a few, perivascular cuffing was noted. Some swelling was noted in vessels not containing the thrombi

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volvement may be general, being found in various parts of the body. Clinical symptoms are rare. There is no known treatment

Obstruction of the Vena Cava

OBSTRUCTION OF THE SUPERIOR VENA CAVA

Obstruction of the superior vena cava occurs secondary to (1) tumors of the thorax (e.g, mediastinal tumors, carcinoma of the bronchus, posterior sulcus tumors); (2) mediastinitis (syphilitic, pyogenic or tuberculous); (3) aortic aneurysms; (4) thrombophlebitis, and (5) constrictive pericarditis

Characteristically there is a history of a feeling of fulness in the head, headache, vertigo and at times mental changes. Engorgement and dilatation of the veins of the head, retinas, neck, arms, upper part of the chest and under surface of the tongue are usually evident. There is conspicuous purplish cyanosis of the face and upper extremities It is especially noticeable when the patient bends forward and persists after he regains the erect position. The eyes are often somewhat prominent Edema of the head, shoulders and arms may occur if the obstruction is sudden Venous pressure in this area is definitely increased, frequently being 200–300 mm. of water.

The differential diagnosis from congestive heart failure is important. In obstruction of the superior vena cava, with the patient supine the venous pressure of the lower extremities is normal while that of the upper extremities is markedly elevated. In congestive heart failure, with the patient supine the venous pressure does not show the same differential between the upper and the lower extremities, often being elevated throughout the circulation.

It is important to determine accurately the site of the thrombus. It may involve any of the veins supplying the superior vena cava, thus accentuating the differential diagnostic problem. If the veins of only one arm are distended and show marked increase in pressure, the thrombus will be found in the axillary subclavian vein.

This is frequently seen in so-called primary axillary venous thrombosis If the veins of the right side of the neck and of the right arm are also involved, the obstructive lesion is probably in the innominate vein. If the evidence of obstruction to venous return flow involves the head, neck and arms bilaterally, the obstruction is in the superior vena cava If there is striking dilatation of the veins over the anterior chest wall and sternum with apparent communications with the branches of the internal mammary vein and without large veins extending down over the abdominal area, the obstruction is probably above the level of the azygos vein. If large veins extend down over the abdomen and there is evidence that the blood flows downward, the chances are that there is an obstruction below the azygos vein which forces the blood to return by way of the *inferior vena cava*

Obstruction of the superior vena cava is always serious The *prognosis, regardless of the type of obstruction, is grave, and in* most cases the outlook is hopeless A few rare patients have *recovered when the obstruction was due to thrombophlebitis* which obstructed but later canalized

When the underlying condition is mediastinal fibrosis or constrictive pericarditis, surgical intervention is justified and may be *successful* Venesection of 500 cc of blood may give temporary relief but will have no permanent effect.

OBSTRUCTION OF THE INFERIOR VENA CAVA

Obstruction of the inferior vena cava is produced by (1) thrombophlebitis or thrombosis, and (2) pressure resulting from ascites, aneurysms, neoplasms or adhesive bands The commonest cause is extension of the thrombus from thrombophlebitis of the femoral and iliac veins

Signs and symptoms include bilateral edema of the legs and prominence of the superficial veins of the legs and abdomen, extending up to the thorax The flow of blood is upward toward the superior vena cava and its branches. Differentiation from conges-

tive heart failure frequently may be made by comparing the venous pressure of the upper and lower extremities. With obstruction of the inferior vena cava, pressure in the upper extremities will be normal or thereabouts, whereas that in the lower extremities will be markedly increased. Ascites may be associated with the condition, but is not due to obstruction of the inferior vena cava alone A common cause of death is extension of the thrombus to and obstruction of the renal veins either by extension of the thrombus beyond their openings or by entrance into the renal veins. I have seen several fatal cases of thrombosis of the renal veins. Albuminuria and hematuria are usually, but not invariably, present.

The prognosis for obstruction of the inferior vena cava is not necessarily poor, although it must always be guarded. If the obstruction reaches the level of the renal veins the outlook is bad. In patients who have an extension of thrombophlebitis into the inferior vena cava from the iliac veins, the thrombophlebitis may subside, canalization may take place, and the patient may live for many years Signs of compensatory dilatation of the superficial leg and abdominal veins will, however, remain.

TREATMENT

Treatment consists in treating the underlying cause. The removal of a large tumor of the pelvis or lower abdomen may greatly diminish the obstructive signs and symptoms. Treatment of the thrombophlebitis is the same as that from any cause

Ligation of the inferior vena cava has been practiced with enthusiasm by some surgeons. The following observations have made us extremely hesitant about recommending this operation. (1) It should not be performed through an inferior vena cava wall which is inflamed. The operation may encourage thrombosis at its site. (2) If it is reserved for thrombophlebitis of the veins of the legs it will rarely be necessary because of availability of anticoagulant and of other modern conservative therapy previously outlined. (3) In many patients we have studied, the long term

results have not been satisfactory Severe varicosities, edema, ulcers and other evidence of chronic venous insufficiency are common. (4) The procedure is major surgery, with risks carefully weighed

Pulmonary Embolism

Of all the complications of *thrombophlebitis*, the most feared is pulmonary or cardiac embolism Not infrequently this occurs before the primary thrombophlebitis is recognized, and in a significant percentage of cases the first embolism may be fatal. Many emboli not only are not fatal but are not recognized unless the clinician is watching carefully for them Even then, they may be found at the autopsy table

If the thrombophlebitis is present in a *small vein* and a portion of or the entire thrombus becomes detached, the resultant pulmonary embolus will probably not be fatal because of its small size If, however, the thrombus in the small vein propagates and extends into a larger vein, following which a portion of or the whole thrombus breaks loose, the condition may be much more serious or, in fact, fatal If the thrombus originates in an iliac or femoral vein and most or all of it breaks loose, the initial embolic phenomenon will quite likely be fatal It should be re-emphasized that a considerable proportion of pulmonary emboli, variously estimated up to 35 per cent, arise from thrombophlebitis in sections of the venous tree where it cannot be recognized clinically and that fatal emboli may develop from any segment.

After a thrombus has been in place in a vein for several days, it is unlikely that the whole thrombus will break loose, although segments of the free propagating tail may break off at any time unless fixed firmly to the vessel wall as a result of organization. Examination of pulmonary emboli in fatal cases almost never reveals evidence of organization of the thrombus, which definitely favors the foregoing hypothesis

Barker, in a study of 343 fatal cases of postoperative pulmonary embolism, failed to discover clinical or autopsy evidence of venous

thrombosis or thrombophlebitis in approximately 40 per cent It seemed probable that in these cases the entire thrombus had become detached to form the embolus In only 15 per cent of the 343 cases was there clinical evidence of thrombophlebitis in any vein prior to death from pulmonary embolism. In only 18 patients (5.2 per cent) was iliofemoral thrombophlebitis diagnosed clinically before evidence of embolism appeared. In 11 of the 18 cases the fatal embolism occurred within the first three days after diagnosis of thrombophlebitis. In the others, postmortem examination disclosed that the embolus in the involved extremity was intact and organized and that the fatal embolism had resulted from detachment of a portion of a fresh thrombus that had formed in the opposite iliac vein without clinical signs of thrombophlebitis.

Pulmonary embolism is rare in chemical thrombophlebitis, although I have seen two patients who died of pulmonary emboli following the injection of a sclerosing solution for varicose veins in the calf Pulmonary embolism from varicose thrombophlebitis is also relatively rare. These cases are usually chronic, and the thrombus is associated closely with the vessel wall. The width of the lumen varies considerably and frequently is narrowed proximal to the site of the varicosity. This does not prevent the development of emboli but tends to discourage it Pulmonary emboli from veins of the upper extremity are rare and I find no record of fatal embolus arising distal to the axillary artery.

The cause of death from pulmonary embolism is not always clear Frequently total obstruction of the pulmonary artery is not found, and only one branch of the pulmonary artery may be occluded. It is believed that some type of shock accompanies the sudden lodging of the embolus and that this immediately or relatively soon causes severe reflex constriction of the pulmonary arterioles and bronchioles which embarrasses pulmonary function over a much wider area than that supplied by the involved artery The effects on the heart may be profound, producing a severe right ventricular strain and failure with acute cor pulmonale There is

apparently also severe reflex constriction of the coronary arteries, and multiple myocardial infarctions involving especially the right ventricle are not unusual. There is an increase of pressure in the right ventricle which interferes with venous return through the thebesian vein and a reduction of flow of the venous blood into the left auricle. Many of these parts have previously been damaged and therefore do not withstand the shock of the combined physiologic disturbance. Many pulmonary emboli apparently disintegrate in a relatively short time, but others propagate rapidly to involve a large portion of the pulmonary arterial tree.

Signs and symptoms.—There is a characteristic severe, stabbing pain in the chest which makes breathing extremely difficult. It is generally considered to be of pleural origin. Although onset of the pain is sudden, there is often reason to believe that the infarction has been in position for as long as 24–36 hours before the pleura is involved and hence before the pain becomes acute. Hemoptysis may follow the onset of pain associated with a cough. Some patients never have this type of pain. Nervousness and apprehension with increased pulse rate are common. There may be no fever, or the temperature may rise as high as 104 F. (40 C.), but it usually subsides rather promptly. A friction rub may be heard, but it is unwise to ask the patient to breathe deeply during a physical examination following one pulmonary embolus since the associated negative pressure may produce another. The typical wedge-shaped shadow often seen in x-rays may be *entirely lacking* or very diffuse. Its absence does not exclude an infarction.

With large emboli the patient shows evidence of *extreme shock*, with dyspnea, cyanosis, pallor, sweating, weakness and a definite fall in blood pressure associated with a weak and rapid pulse. Pain in the neck may be prominent and *pulsating*. Vomiting may occur. Scattered or numerous moist râles are frequently heard. Pleural pain is increasingly severe, and *hemoptysis* is prominent. X-ray study reveals *extensive* clouding of the lung, and not infrequently

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fluid accumulates. The diaphragm on the affected side may be elevated

It is important that the severe form be clearly differentiated from acute coronary thrombosis and acute lobar pneumonia Confusion with coronary thrombosis is relatively common because the electrocardiographic changes are somewhat similar. However, they can usually be differentiated The characteristic pattern of acute cor pulmonale associated with severe pulmonary embolism follows The S wave in lead I is prominent and often widened. In lead II the S-T interval usually takes off below the isoelectric line. The T wave is diphasic, isoelectric or upright In lead III the RS-T segment is not elevated or is elevated slightly. Characteristically the T wave is inverted and may be covelike In lead CFIV the S-T interval is usually unchanged and the T wave may be either negative or positive In lead CF_2 the T wave is usually negative. In the Wolferth lead the normally inverted T wave is upright. The presence of these changes depends to a large degree on the size and location of the pulmonary embolism. Electrocardiographic tracings must be made repeatedly because the changes may not appear for 48 hours and are usually transient, returning to normal somewhat more rapidly than one would anticipate for equally marked changes on the basis of a coronary occlusion.

The changes just described, when carefully analyzed, usually are not suggestive of coronary occlusion with myocardial infarction The possibility that pulmonary emboli may arise from the right side of the heart must not be forgotten. This most frequently occurs from fibrillating hearts but may be secondary to endocarditis and to myocardial infarction with development of a mural thrombus

Prognosis.—If the embolism is massive enough, death may occur within minutes. At the other extreme is absence of any reaction, with no signs or symptoms The course with nonfatal emboli that cause definite symptoms lasts four to 10 days, during which the patient shows steady improvement. Occasionally pleural

pain persists for a long time. Multiple emboli are common and must be anticipated. Secondary infection or abscess may complicate the picture, and for this reason it is usually wise to give large doses of penicillin for prophylaxis.

Treatment.—In general, like lightning, the embolism which is recognized does not kill; but, unlike lightning, this condition does often strike more than once in the same place. The most important aspect of therapy, therefore, is to eliminate the source of the embolism. This is done by ligation and anticoagulant therapy if the thrombophlebitis is in the veins of the legs. Otherwise one must lean on anticoagulant therapy alone, whether the source be in the veins or in the heart. For the technic of anticoagulant therapy, see earlier pages in this chapter.

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CHAPTER XXI · Acute Axillary or Subclavian Venous Thrombosis

ACUTE THROMBOSIS of the axillary or subclavian vein occurs relatively infrequently and in most cases independently of thrombophlebitis elsewhere in the body.

Etiology

It usually is secondary to trauma of mild but repetitive nature and often becomes a medicolegal or industrial compensation problem For example, I have seen the condition in several individuals who worked as laborers shoveling gravel or dirt. Another patient worked at moving large sheets of cardboard, with a co-worker supporting the opposite end, from one pile to another. In a woman, axillary venous thrombosis developed from straining as she attempted to raise a heavy window that was stuck. In another patient it developed after he had played a strenuous baseball game. It has incapacitated professional baseball pitchers It is fairly common in acrobats, especially those who work on the trapeze and horizontal bars We have had the opportunity of studying several such cases

Clinical Manifestations

Characteristically, attention is first attracted to the condition by sensations of stiffness of the arm and swelling of the hand. In several cases a friend or co-worker called the patient's attention

to swelling of the hand. Pain in the axillary area is not conspicuous; a few patients complain of a dull ache. The extremity soon begins to feel heavy when it is allowed to remain in the dependent position.

Examination reveals a swollen, puffy hand, often with pitting edema, milder swelling of the arm to the shoulder, and a dusky cyanosis involving the forearm and hand, seen in most patients but not all. There is increased prominence of the superficial veins



[illegible] thrombosis of right [illegible] rotrast return [illegible] rast returning [illegible] llateral veins [illegible]

of the upper arm, deltoid area and, particularly, the pectoralis region (Fig. 97) This represents an attempt of the collateral circulation to compensate for the blockage of the vessels. There is often an increase in the surface temperature of the extremity. A cordlike mass is palpable if the thrombosis extends from the axillary down into the brachial vein. It is not palpable in all cases

The condition, which arises suddenly following mild repeated exercise or sudden mild strain (apparently produced by pinching of the subclavian axillary vein between the posterior surface of the

clavicle and the anterior surface of the first rib or between certain muscle groups) must be differentiated from blockage of the subclavian veins or superior vena cava by a mediastinal tumor or mass. X-ray study of the mediastinum and venography by injection of a radiopaque substance into the veins of the cubital space may clarify the diagnosis Figure 97 clearly shows that when the main axillary subclavian trunk is unobstructed the dye proceeds rapidly through the main channel without involving the collaterals. With blockage the collateral circulation is used and the dye does not pass through the main trunk

Why a patient can continue at the same type of occupation for many years before suddenly developing this condition is not clearly understood. Many of the patients I have seen have been middle aged or older. It is possible that with aging changes in the relationships of the muscles of the shoulder girdle permit pinching or a tendency to sagging of the clavicle against the first rib. Some cases do occur in persons under age 25.

This type of thrombosis has considerable importance in industry because return of the patient to his former occupation or one requiring similar muscular action almost invariably precipitates another attack, and therefore rehabilitation to another type of work must be seriously considered Rudolph Matas, who described the condition in detail, emphasized this phase of the problem. One of our patients who developed this syndrome while using a shovel had a relapse 10 months later when he returned to the same work. He was then taught to do automobile upholstery, which seemed a sufficiently different type of work, but the strain of pulling the material tight caused another relapse

Treatment

Rest with the arm elevated is essential to prevent increase of the edema and overdilatation of the compensatory venous channels Hot moist packs are applied over the entire arm to the shoulder,

and anticoagulant therapy is administered (p 423). Anticoagulant therapy usually should be given for three or four weeks Procaine blocks of the cervical area have been used to induce relaxation but are seldom necessary Ligation or section of the sub-



FIG. 98—A Foley sleeve worn on an arm swollen as a result of axillary venous thrombosis (From Medichrome Series MM—Vascular Diseases, by I S Wright and W T Foley)

clavian vein has, in our experience, proved to be detrimental because edema is aggravated

The continued wearing of a specially made elastic sleeve (Fig 98) designed by my associate, W. T. Foley, is an important part of the follow-up therapy. In some cases it definitely decreases the lymphedema. It may be necessary for the patient to add a rubber surgical glove if the fingers are swollen This compression may be necessary for from three months to a year and in some cases in-

definitely. It is equally helpful for lymphedema of the hand and arm.

Even in the most favorable circumstances the ultimate prognosis for this type of thrombosis is not very good in terms of complete immunity to relapse. In some patients there is a persistent tendency for the hand to become edematous on dependency. The risks of extension of the thrombus into the superior vena cava and of the development of pulmonary or cardiac emboli seem to be much less than with other types of phlebothrombosis and thrombophlebitis, although occasionally these complications do arise.

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disease common to flagpole sitters—swollen legs. Large blisters developed on his feet from which fluid constantly dripped.

There would seem to be three points of possible obstruction of the vessels: (1) the popliteal space, where the knee folds; (2) the posterior surface of the thigh, where the pressure from sitting interferes with the venous and lymph return flow, and (3) the fold of the groin, where obesity and tight underwear may cause enough pressure to impede return flow.

I have treated six women in whom this syndrome with thrombophlebitis developed after long automobile trips during which they wore tight girdles that folded tightly in the inguinal region. The same syndrome developed in two after flying from Rio de Janeiro to New York sitting up with a tight girdle on. Since the first edition of this book I have seen numerous additional examples of this syndrome after air, train or automobile travel. Most of them have been in women who wore girdles during these trips. During travel that requires prolonged sitting, *the necessity of moving frequently and removing girdles and other clothing that binds at the key points should be emphasized.* Progressive travel agents of air, bus and rail lines would do well to advise their patrons regarding these preventive measures.

Although both venous and lymphatic channels may be temporarily obstructed, it is probable that the only serious potentiality is actual thrombosis of the venous channels. Most patients recover within a day or two of rest and normal activity. Our patients in whom serious thrombophlebitis developed have recovered following treatment. Cases have been reported in which fatal emboli followed the development of shelter foot, but I have not seen such a case. Dr. M. C. Thorner has reported to me the case of a man who developed a serious pulmonary embolism after a three day ride on a sit-up train. Anticoagulants have been used when indicated.

Treatment, if the condition is mild, *resolves itself* into elevation of the legs for a few hours and moderate activity. If there is evi-

CHAPTER XXII Dependency Edema

KNIGHT DESCRIBED the edema observed in individuals who had been sitting up all night in air raid shelters, especially those who had used portable beach chairs constructed with a rod that pressed on the posterior surfaces of the thighs. He called the condition "shelter foot."* This edema is particularly likely to occur in women with soft fatty tissue of the thighs The exact mechanism is not clear, but it is thought to be due in part to thrombosis or at least to pressure obstruction of the small, and in some cases larger, veins of the posterior surfaces of the legs. Obstruction of the lymphatic channels no doubt also plays an important role. The edema may be mild or severe It is the pitting type and may involve only the foot or extend as high as the groin. If predominantly lymphatic, it is pale; if venous, it is dusky.

We have seen at least 20 patients with a clearcut picture of a similar edema that followed prolonged sitting with the feet dependent They had traveled for 24 or more hours in a "sit-up" train, sat for 12–20 hours during a plane trip or taken an automobile or bus trip lasting 10–20 hours The development of this syndrome on long train, automobile or plane trips has received little or no attention in the medical literature.

Perhaps the most unusual example of this phenomenon to be recorded was that of a professional "pole sitter," who sat on top of a pole 52 days, 13 hours and 58 minutes to break all previous records. It is recorded that he thereafter was laid up in bed with a

*Dependency edema now seems a preferable term for this syndrome

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CHAPTER XXIII Varicose Veins; Chronic Venous Insufficiency

VARICOSE VEINS

BY VARICOSE VEINS is meant simply dilated veins. The dilatation may occur anywhere in the body.

ETIOLOGY

Primary varicose veins develop spontaneously. It is believed that in most cases there is a hereditary weakness of the walls or the valves of the veins Some develop as a result of congenital arteriovenous anastomoses (discussed in Chapter XII). This type of varicosity occurs when increased pressure is exerted within the weakened lumen on prolonged standing, coughing, sneezing, lifting or straining or when there is increased lower abdominal or pelvic pressure against the inferior vena cava or iliac veins with abdominal obesity, large tumors, pregnancy and similar conditions.

Primary varicose veins are attributed to an inherent weakness of the venous lumens because certain inciting factors lead to their appearance in some individuals and not in others. Furthermore, the data on the hereditary factor are impressive. Approximately 40 per cent of all individuals with varicose veins have a family history of varicosities The following family history from my practice is a striking example

1. The mother had varicosities most of her life. She had five chil-

dence of thrombophlebitis, the treatment is that described in Chapter XX.

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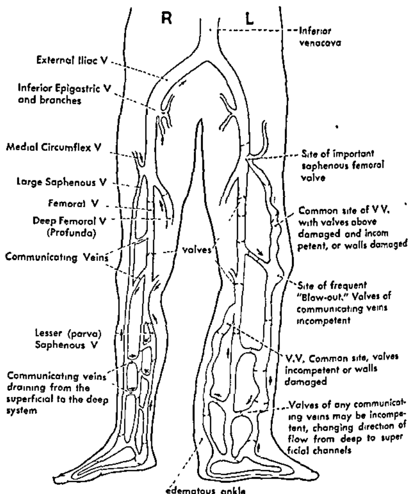


FIG 99—Schematic drawing showing *R*, normal directions of venous flow [illegible]

dren at ages 20, 22, 23, 25 and 32 She wore elastic stockings for 20 years and died at 62 of hypertensive cardiovascular disease.

2 The father had mild varicosities for many years He died at 64 of carcinoma of the sigmoid

3 A daughter, 47, has had three normal pregnancies. Varicosities that developed (without phlebitis) during the first pregnancy were aggravated by the subsequent pregnancies

4 A son aged 45 has had varicosities since age 30 and two mild episodes of thrombophlebitis He had a hemorrhoidectomy at age 42.

5 A daughter aged 44, unmarried, has had severe varicosities for 20 years They are aggravated by prolonged standing.

6 A daughter aged 42 had a twin pregnancy at age 25, followed by severe varicosities and chronic indurative edema A double saphenous ligation performed at 39 did not improve the condition

This history is unusually instructive Two parents with varicosities had two daughters in whom varicose veins developed following pregnancy, one daughter with varicosities *who had never been pregnant* and a son with varicosities. This strongly suggests that inherited weakness of the veins was responsible, rather than other factors such as pregnancy

We have seen several individuals who had congenital absence of the valves of the veins communicating between the deep and the superficial system proved by pathologic studies This is probably a rare condition but does lead to varicosities of the superficial veins. The clinical diagnosis of congenital absence of the valves of communicating veins may be suspected but can be established only on histologic examination of the communicating branches

The incidence of varicosities is definitely higher in females than in males In study of a large group of department store employes working at similar occupations, Lake, Pratt and I found a conspicuously higher incidence of varicose veins in women than in men who had been at the same occupation, such as standing behind a counter, over an average of 17 years At first it was thought that this might be due to the fact that many women had been pregnant, but when the pregnancy group had been removed from the statis-

tical series the women still showed a much higher percentage of incidence than the men (Tables 18 and 19).

Some writers have advanced the hypothesis that the difference *in sex incidence is in part due to endocrine factors—a rather indefinite term.* We suggested that repeated congestion of the pelvic area during menstruation may have a role, and that the rather thin, nonmuscular walls of the veins have relatively less support from the surrounding soft tissues in women than in men.

TABLE 18.—INCIDENCE OF VARICOSE VEINS *

		Varicose Veins	
		No.	%
Men	305	125	41
Women			
Never pregnant	133	89	67
One or more pregnancies	98	78	79

* From Lake, M, Pratt, G H, and Wright, I S, J A M A. 119 692, June 27, 1942

TABLE 19.—INCIDENCE OF VARICOSE VEINS BY SEX AND OCCUPATION *

	Men		Women (Never Pregnant)	
	Total	With V V	Total	With V.V
Standing	89	36 (40%)	63	47 (74%)
Walking	129	53 (41%)	28	19 (68%)
Sitting	40	20 (50%)	42	23 (57%)
Climbing stairs	47	16 (34%)	0	

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Secondary varicose veins are due principally to thrombophlebitis which causes damage to the walls of the vein and destruction of the valves of the involved vein as well as of the communicating veins between the deep and the superficial system. Destruction of each valve throws additional back pressure on the walls of the vein peripheral to that valve and on the valve below it. If a number of valves are destroyed in any area, the total head of pressure built up when the patient is erect increases greatly and with it the tendency to varicosities.

Secondary varicose veins can, in all probability, develop without congenital weakness of the vein walls in the presence of sufficient back pressure, as in some instances of pregnancy, abdominal

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and severe night cramps. Infection may be a factor when the lesion is complicated by edema, eczematoid dermatitis or fungus infection.

It is not commonly recognized that massive varicose veins in the legs may aggravate cardiac failure to a marked degree One case may be cited as an example.

A man, 60, had had rheumatic heart disease with a double mitral lesion for many years. For two years heart failure had been intractable Little response was noted to digitalis, mercurial diuretics, ammonium chloride, aminophylline or a low salt diet. Relative comfort could be obtained by rest in bed, but almost immediately upon arising acute dyspnea and precordial pain became unbearable. Examination showed the heart size markedly increased. Characteristic murmurs of mitral stenosis and insufficiency were heard There were hepatic enlargement and pronounced edema of both ankles Most striking were extremely large varicosities of the veins of both legs In many areas they were an inch in diameter It was obvious when the patient stood that a large

provement was to eliminate the great venous pool. This was done by Dr Jere Lord, who operated on one leg at a time Although the patient had a somewhat stormy time after the second operation from the viewpoint of cardiac failure, the end results were excellent. He wears knee-length elastic stockings for additional support. Dyspnea and precordial pain on standing have disappeared and his status is generally quite satisfactory on a cardiac régime that previously was ineffectual

Examination discloses a variety of pictures ranging from the small spider or rocket-burst type of varix, common in women, especially obese ones, to varices of different sizes involving branches of the saphenous vein up to huge tubes and saccular varices with numerous bulging "blowouts" at the points where incompetent communicating veins discharge into the superficial system instead of carrying the blood into the deep system. Edema,

pitting and nonpitting, eczema, fungus infection, pigmentation and varicose ulcers are frequent complications. The ulcers may be

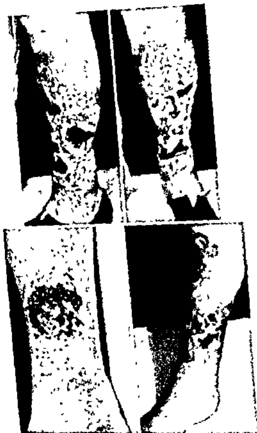


Fig 100—Serious ulcers produced by chronic venous stasis resulting from long standing varicose veins (Courtesy of Dr. Gerald H Pratt)

indurated and chronic (Fig 100), some in our series being open for as long as 25 and even 46 years

The site of the venous obstruction and of incompetent valves may be determined by various tests, among them the Brody-Trendelenburg, Perthes and Pratt tests (For details, see Chapter II.)

The information gained is important for successful ligation and injection treatment. Venograms are rarely helpful.

PREVENTION AND TREATMENT

In many instances varicose veins can be prevented or reduced to a minimum by the avoidance of constriction by tight garters, girdles and other clothing which tends to obstruct venous return flow and thus increase venous pressure. Care and thought should be given to the prevention of varicose veins during pregnancy. With evidence of their development the patient should be kept from prolonged standing Elimination of tumors and other obstructive lesions in the pelvis and abdomen may relieve the tendency to varicosity. A supportive or elastic bandage or stocking worn by a patient with varicosities when he is going to be on his feet for long periods will prevent aggravation of the condition. By means of an elastic support the venous flow is forced into the deeper system so that the deep veins can handle the return flow without further pressure on the superficial ones. The foot of the bed should be elevated 10–12 in. to minimize venous pressure during the sleeping hours.

The most important therapeutic measure for varicose veins is their surgical ligation, with stripping technic for removal if necessary. The injection of sclerosing solutions to produce chemical thrombosis is used as adjuvant therapy. Many technics for injection and surgery have been presented since the time of Galen. The objective in all instances is to obliterate permanently that portion of the venous tree under treatment. Oftentimes injection per se does not accomplish the purpose, for although there is an immediate obstruction, within one month to five years recanalization takes place and the varicosity returns.

Multiple ligation at suitable levels appears to be most satisfactory treatment. In the presence of severe varicosity of one of the saphenous veins, ligation and resection or stripping of the major

segment of the vein is the most commonly used technic. After the reaction and resulting obliteration of the treated portion of the venous tree, search should be conducted for any varices or blowouts caused by incompetence of the valves of communicating veins and branches. These may be treated by local injection or ligation according to indications.

Injection may be used for very small varicose veins but, as previously mentioned, is seldom permanently satisfactory for larger varices. Recurrences involving new sets of veins are common after all procedures, so it is well not to give the patient a "lifetime guarantee" that he will not have more varicose veins.

There are some contraindications to the use of sclerosing solutions. Sometimes they cause local and occasionally generalized reactions. Serious diseases, including cancer, Bright's disease, congestive heart failure, myocardial infarction, acute cellulitis or lymphangitis of the leg, severe blood dyscrasias, tuberculosis and serious hepatic disorders, contraindicate sclerosing therapy either because the general prognosis does not warrant the local treatment or because it may further complicate the general condition. In the presence of certain other diseases it is necessary to treat the general condition first and be certain that it is under control before a sclerosing solution is injected. These include hypothyroidism, diabetes, any acute infectious disease and active thrombophlebitis. In all cases careful thought should be given to the patient's general condition.

Quinine and urethan may produce the symptoms of cinchonism, including transitory flushing, dizziness, tinnitus and a sensation of warmth in the throat, nausea, vertigo and intestinal or uterine spasm and, in some women, vaginal bleeding. Major allergic crises have occurred with circulatory collapse especially in hypertensive patients.

Some patients are sensitive to sodium morrhuate, which is the most generally used sclerosing solution. I have seen a sudden death

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PREVENTION AND TREATMENT

In many instances varicose veins can be prevented or reduced to a minimum by the avoidance of constriction by tight garters, girdles and other clothing which tends to obstruct venous return flow and thus increase venous pressure Care and thought should be given to the prevention of varicose veins during pregnancy. With evidence of their development the patient should be kept from prolonged standing Elimination of tumors and other obstructive lesions in the pelvis and abdomen may relieve the tendency to varicosity A supportive or elastic bandage or stocking worn by a patient with varicosities when he is going to be on his feet for long periods will prevent aggravation of the condition By means of an elastic support the venous flow is forced into the deeper system so that the deep veins can handle the return flow without further pressure on the superficial ones The foot of the bed should be elevated 10–12 in. to minimize venous pressure during the sleeping hours

The most important therapeutic measure for varicose veins is their surgical ligation, with stripping technic for removal if necessary. The injection of sclerosing solutions to produce chemical thrombosis is used as adjuvant therapy Many technics for injection and surgery have been presented since the time of Galen. The objective in all instances is to obliterate permanently that portion of the venous tree under treatment. Oftentimes injection per se does not accomplish the purpose, for although there is an immediate obstruction, within one month to five years recanalization takes place and the varicosity returns

Multiple ligation at suitable levels appears to be most satisfactory treatment. In the presence of severe varicosity of one of the saphenous veins, ligation and resection or stripping of the major

segment of the vein is the most commonly used technic. After the reaction and resulting obliteration of the treated portion of the venous tree, search should be conducted for any varices or blowouts caused by incompetence of the valves of communicating veins and branches These may be treated by local injection or ligation according to indications

Injection may be used for very small varicose veins but, as previously mentioned, is seldom permanently satisfactory for larger varices Recurrences involving new sets of veins are common after all procedures, so it is well not to give the patient a "lifetime guarantee" that he will not have more varicose veins.

There are some contraindications to the use of sclerosing solutions. Sometimes they cause local and occasionally generalized reactions Serious diseases, including cancer, Bright's disease, congestive heart failure, myocardial infarction, acute cellulitis or lymphangitis of the leg, severe blood dyscrasias, tuberculosis and serious hepatic disorders, contraindicate sclerosing therapy either because the general prognosis does not warrant the local treatment or because it may further complicate the general condition. In the presence of certain other diseases it is necessary to treat the general condition first and be certain that it is under control before a sclerosing solution is injected. These include hypothyroidism, diabetes, any acute infectious disease and active thrombophlebitis In all cases careful thought should be given to the patient's general condition.

Quinine and urethan may produce the symptoms of cinchonism, including transitory flushing, dizziness, tinnitus and a sensation of warmth in the throat, nausea, vertigo and intestinal or uterine spasm and, in some women, vaginal bleeding Major allergic crises have occurred with circulatory collapse especially in hypertensive patients.

Some patients are sensitive to sodium morrhuate, which is the most generally used sclerosing solution. I have seen a sudden death

that was attributable to it. It is therefore important that a patient be given a test dose of 0 2–0.5 cc. intravenously 12–24 hours before treatment

For injection into a small vein without ligation, the patient stands on a table in the best position to permit the physician to reach the vein. The average dose is 2–4 cc of a 5 per cent solution of sodium morrhuate or of 3½ per cent of sodium ricinoleate in patients sensitive to sodium morrhuate Treatments may be given every day. If the *local* reaction is unduly severe, 2 cc. may be given twice a day. With the appearance of any systemic reactions whatever, further injections should not be given.

A local chemical phlebitis is desired to obtain satisfactory obstruction Injection is usually made with a 2–5 cc. syringe using a 25 gauge needle. It is important that the needle be free in the lumen of the vein so that surrounding tissues will not receive the irritating substance Therefore the plunger should always be drawn back to make certain that venous blood returns easily before the solution is injected. Any local swelling of the skin during the injection indicates that the solution is leaking into the surrounding tissues and the injection should be stopped immediately and a tight binder applied to the area Usually the patient will complain of pain if the solution is spilled into the tissues Injection of 1 or 2 cc. of physiologic saline solution may dilute the sclerosing solution in the tissues if this seems necessary.

After injection of the sclerosing solution a sterile gauze pad is applied to the site of injection and moderate pressure maintained by adhesive tape or a bandage. The pad should be worn for two or three hours

Nonallergic substances which are sclerosing include dextrose, invert sugar and invertose

The technic of surgical ligation of veins is not within the scope of this volume.

The reader who wishes further discussion of the subject of varicose veins is referred to the excellent monographs of Foote of England, Martorell and Piulachs of Spain and Pratt of this country

Chronic Venous Insufficiency—Varicose Ulcers

ETIOLOGY

Chronic venous insufficiency may be due to thrombophlebitis which has involved either small segments of the veins of the legs (less frequently of the arms) or larger segments of the venous tree up to the iliofemoral or even inferior vena cava segments. It may also follow the development of varicose veins from any cause or may be due to congenital or acquired arteriovenous anastomoses which cause increase in pressure and dilatation of the veins.

The development of chronic insufficiency following thrombophlebitis or the appearance of congenital varicose veins rests on the damage to the valves of the larger vessels or the absence of these valves. The mechanism is the establishment of back pressure, with stasis and lack of proper downward gradient from the arterial to the venous side of the minute vessels In addition, with an attack of thrombophlebitis and damage of many of the small veins, their walls become more permeable to tissue fluids Homans has also emphasized the damage of the lymphatic channels which accompanies that of the veins and which may result in severe interference with return of lymphatic fluid from the extremity

CLINICAL MANIFESTATIONS

The condition is characterized by edema and dusky cyanosis, dilatation and prominence of the veins, and chronic ulceration in some cases The edema may not be present when the patient gets up in the morning but progressively accumulates during the day. In some patients, however, the edema does not disappear during the night This becomes increasingly serious with the passage of time and the laying down of fibroblastic cells in the intercellular spaces as a result of stagnation of fluid Dusky cyanosis appears on dependency of the extremity The dilatation and prominence of the veins vary widely. Chronic ulcers develop around the ankle in some but not all cases.

Most patients have conspicuous varicosities In some the veins are extremely large. In others there are many small plexuses of veins which are superficial, but tests disclose marked insufficiency of the deep veins This is also manifested by the development of discomfort in the extremity after prolonged dependency and relief on elevation. The discomfort is most severe after long periods of standing. It is relieved by walking, especially if the patient is wearing an elastic stocking to support the veins and aid them in moving the blood along by pressure on muscular contraction.

The severity of the condition depends to a considerable extent on postphlebitic care. Patients who wear elastic support for the first year or two after an attack of thrombophlebitis and who sleep with the foot of the bed elevated will have far less chronic venous insufficiency over a period of years than those who do not take these precautions. It is the physician's responsibility to see that the patient is instructed and encouraged in this regard

With the passage of years the edema becomes more fixed with fibrous tissue proliferation and becomes the nonpitting type. The tissue then is especially susceptible to secondary infection. Not infrequently, repeated erysipeloid attacks involve the extremities, sometimes serious, with high fever and severe general reactions. Eczematoid eruptions and ulcers are often seen, and secondary fungus infection is a common and often protracted complication The ulcers may become deep, indurated and chronic; I have seen a number that had been present for more than 25 years and one for 46 years.

Pigmentation of the skin is often present in the regions with chronic edema and congestion, but rarely does the physician observe these areas carefully enough to note that many petechial hemorrhages may be present, particularly after prolonged standing. These extravasations of blood into the tissue leave hemosiderin, which is responsible for the pigmentation. The petechial hemorrhages are usually due to the back pressure which, becoming too great for the damaged walls of the minute vessels, causes them

to rupture. Some patients have the additional complication of subclinical or clinical scurvy. The inclusion of as much as 300 mg. of vitamin C daily to the diet has resulted in almost complete cessation of the hemorrhages and in some cases healing of otherwise intractable ulcers (Fig 101). To determine the significance of

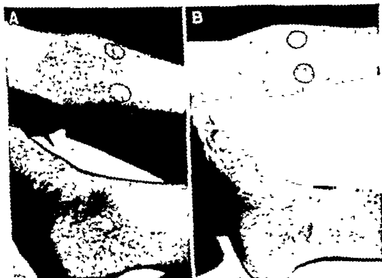


FIG 101—Varicose veins and avitaminosis C *A*, before therapy Capillary fragility test showed over 150 petechiae, plasma ascorbic acid content was 0 27

such generalized disturbances in any case it is wise to make capillary fragility tests (Chapter II) and study the vitamin C blood level.

TREATMENT

The treatment of chronic insufficiency includes the ligation, if practical, of veins which are extensively varicosed, elevation of

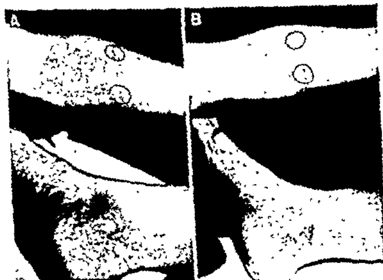
Most patients have conspicuous varicosities. In some the veins are extremely large. In others there are many small plexuses of veins which are superficial, but tests disclose marked insufficiency of the deep veins This is also manifested by the development of discomfort in the extremity after prolonged dependency and relief on elevation The discomfort is most severe after long periods of standing It is relieved by walking, especially if the patient is wearing an elastic stocking to support the veins and aid them in moving the blood along by pressure on muscular contraction.

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[illegible] 100 mg three times a day for two weeks Capillary fragility test showed eight peterhiae, plasma ascorbic acid content was 1.2 mg per cent. The ulcer of the *malleolus* was healed.

such generalized disturbances in *any* case it is wise to make capillary fragility tests (*Chapter II*) and study the vitamin C blood level.

TREATMENT

The treatment of chronic *insufficiency* includes the ligation, if practical, of veins which are *extensively* varicosed; elevation of

the foot of the patient's bed 10–12 in ; the wearing of a knee-length elastic stocking at all times when the patient is not in bed, and the avoidance of prolonged standing without intervals during which the leg can be elevated. A fungus infection may be treated by potassium permanganate 1:5,000 soaks for 30 minutes every other day or with other fungicides. Tests for capillary fragility may suggest that vitamin C or rutin may aid in the prevention of petechial hemorrhage and ulcers. An eczematoid or other skin reaction should receive appropriate local therapy

In the presence of *varicose ulcers* the treatment should be intensified. The ulcers are usually slow to heal while the patient is ambulatory. The first step should be elevation of the leg for drainage and reduction of edema. The ulcer should be exposed to the air to dry unless this is too painful, in which case wet dressings of penicillin in 0.05 per cent solution or tyrothricin may be used. A varicose vein draining out of the ulcer should be ligated before a permanent result can be hoped for Skin grafts may be used for large ulcers, but if draining veins are not competent or ligated the results are usually poor. Dried human blood cells (Lyocyte powder) have been recommended to aid tissue regeneration. This preparation is dusted on the ulcer once or twice daily. Our experience with this substance has been encouraging, but conclusive evaluation is difficult ACTH and cortisone are being studied for their effect in encouraging epithelization.

Other technics that have proved useful are the application of rubber sponges, bound firmly over the ulcer area for five to 25 days by means of a rubber or elastoplast bandage; Unna's paste cast (when edema is not present), changed each five to 10 days, and mecholyl ion transfer three times a week.

Whatever the preliminary treatment, experience has demonstrated that elastic stockings or rubber bandages should be worn for one or more years whenever the patient is out of bed, provided the skin can tolerate them. Sometimes chronic edema prevents their use for long periods.

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CHAPTER XXIV Hypertensive Ischemic Ulcers of the Leg

IN SOME CASES of hypertensive disease the arterioles of the skin become sclerotic, just as are the retinal vessels, and small areas of the skin may develop infarction Rarely, the ischemic infarct breaks down in the form of an ulcer of the skin In 1945 Martorell described four cases of ulcer of the lower leg associated with hypertension. Biopsy revealed arteriolar changes which produced ischemic areas in the skin Such lesions had been described by Haxthausen in 1940 Hines and Farber of Mayo Clinic described 11 such ischemic ulcers, all in the lower legs of women with hypertension and arteriolosclerosis In each case the skin of the leg was normal elsewhere and did not show edema There was no evidence of varicose veins or thrombophlebitis and the large vessels were patent and actively pulsating

The first abnormality noted is a painful red plaque, which becomes blue and then purpuric in a few days. A small flat area of bluish discoloration, usually over a malleolus, develops into a hemorrhagic bleb and breaks down to form a superficial ulcer which slowly enlarges to a diameter of 1–7 cm The pain is moderately severe Granulation is not active and little or no exudate appears The ulcer may heal in six months with rest of the extremity and allowing the ulcer to dry ACTH, used cautiously because of hypertension, may hasten epithelization of some

In tissue sections the arteriolar walls are seen to be thickened

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venous circulation, the severe retinal changes, the characteristics of the ulcer and the presence of severe hypertension, the diagnosis of hypertensive ischemic ulcer of the leg was made.

The patient was hospitalized and the leg was placed in the horizontal



FIG 102 —Hypertensive ischemic ulcers in a man, showing sites of former ulcers over right anterior tibial area and right internal malleolus, and present ulcer over left internal malleolus

position The ulcer, which was a purplish, moist, sharply demarcated lesion, was soaked daily in normal saline for a half-hour, followed by the application of *dried human red cells (Lyocyte powder)* to cover the lesion. The ulcer healed to about one-half its original size in 10

and the lumens narrowed. The number and size of the nuclei and the media are increased, with hyaline degeneration. Intimal proliferation and periarteritis are also noted.

It is important that these ulcers be clearly differentiated from those of pernio, which are apt to be deeper and more painful, occur in cold weather and rarely heal until hot weather arrives

The first case of this syndrome recognized by us was in a man. No doubt other cases in males will be identified in the future. A typical history follows.

The patient, aged 41, first seen April 8, 1947, had been known to have high blood pressure for at least five years. During this period it had averaged approximately 200/140-130 and become increasingly severe. About two years after the hypertension was diagnosed, ulcers developed that involved the anterior tibial portion of the right leg. The ulcers first appeared as an area of redness of the skin ranging from 1 to 8 cm across Following this, bleb formation took place. The skin peeled off and ulcers developed which lasted from six months to two years In each instance the lesion was extremely painful. The scars persisted (Fig 102).

Ten days before we saw him he had a transient cerebral vascular spasm with paralysis, numbness and tingling of the left side of the body which lasted a few hours On examination the blood pressure was 205/140 He was a plethoric individual who appeared older than his age The heart was enlarged to the left. The aortic second sound was greater than the pulmonic second sound and was sharp. Examination of the fundi showed marked retinal arteriolarsclerosis. There were no hemorrhages or exudate

Examination of the lower extremities revealed scars of the former ulcers and on the left leg an open ulcer about 1¾ in in diameter covering the medial malleolus There was no pallor on elevation or rubor on dependency of the extremities. The dorsalis pedis and posterior tibial arteries were easily palpable. Oscillometric readings were within normal limits:

	Right	Left
Foot	0 5	0 3
Above ankle	3 0	2 1

There was no evidence of venous insufficiency of either extremity. No varicose veins could be seen. In view of normal major arterial and

venous circulation, the severe retinal changes, the characteristics of the ulcer and the presence of severe hypertension, the diagnosis of hypertensive ischemic ulcer of the leg was made.

The patient was hospitalized and the leg was placed in the horizontal



FIG 102—Hypertensive ischemic ulcers in a man, showing sites of former ulcers over right anterior tibial area and right internal malleolus, and present ulcer over left internal malleolus

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days, then ceased to improve. Therefore typhoid vaccine was given intravenously according to the technic described on page 202. Healing progressed rapidly and was complete exactly 28 days after beginning treatment. Pain, which had been almost unbearable, was completely eliminated He returned in 1950 with a larger ulcer of the same type Blood pressure then averaged 260/150. The ulcer healed in eight weeks with rest in bed and ACTH given cautiously because of his high blood pressure

We have since observed three additional cases which we felt met the criteria for this diagnosis, and other workers have reported additional examples of this syndrome (see the references).

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CHAPTER XXV: Polycythemia Vera as a Vascular Disease

ALTHOUGH POLYCYTHEMIA vera is essentially a hematogenous disease, it frequently produces syndromes related to vascular disease. For this reason, discussion of this combination of conditions is believed appropriate. Numerous patients with polycythemia vera have first been referred to specialists in vascular diseases because of the occurrence of an arterial occlusion or, more frequently, thrombophlebitis.

In several instances there has been confusion in the diagnosis between polycythemia and thromboangiitis obliterans The following is a case in point.

A man 37 years old was hospitalized with a diagnosis of thromboangiitis obliterans. Physical examination disclosed gangrene of the toes of the right foot associated with marked rubor on dependency. The dorsalis pedis artery was occluded and there were classic local signs of thromboangiitis obliterans. It was noted, however, that his complexion was extraordinarily ruboric

Although the spleen was not palpable, blood study revealed red cells 8,560,000; hemoglobin content 158 per cent; hematocrit 69 per cent. It was necessary first to treat the polycythemia vera. This was done by means of phlebotomy and the administration of 0.1 Gm. of acetylphenylhydrazine three or four times per week. By this approach the gangrenous area healed and the patient was in good health from 1931 until 1940, when he died of pneumonia. Constant guidance was required regarding the dose of acetylphenylhydrazine.

Perhaps the commonest vascular complication of polycythemia

vera is thrombophlebitis All patients with phlebitis should have a complete blood study. On numerous occasions we have determined the correct diagnosis of polycythemia because of a red blood cell count as high as 11,000,000–13,000,000 which had not previously been noted owing to the physician's concentration on the phlebitis and his failure to make a complete blood count. Thrombophlebitis, however, is apparently not dependent solely on the height of the red blood cell count Repeated thrombotic episodes may occur in some patients with the red cell count well below 5,000,000. There appears to be what might be termed a critical level in each patient I have had the opportunity of studying a most remarkable example of this.

In a man with polycythemia vera, with an original red cell count over 9,000,000, extensive thromboses developed each time the red blood cell count was allowed to exceed 4,000,000 When the count hovered around 3,000,000 no thrombi occurred, he felt well and was able to carry on his occupation as butcher This phenomenon was repeatedly demonstrated It was first discovered accidentally when an overdose of acetylphenylhydrazine brought the red cell count to 2,500,000. Then for the first time he was completely free from thrombotic episodes. Because of the low red cell count he was given a transfusion and acetylphenylhydrazine was withheld. When the count reached 4,000,000 thrombosis recommenced, with severe involvement of the brachial vein. It has been necessary therefore to keep the red cell count below 4,000,000 over a period of years

I know of no other reported case of this type. The explanation is not clear, but the case suggests that the thrombosing tendency in polycythemia vera may depend to some degree on factors other than the increase of cell content. This appears to be an important concept to bear in mind.

Arterial thrombosis is another common and serious complication of polycythemia vera. Where the thrombi occur is purely a matter of chance. The cerebral or coronary arteries or those of the extremities may be involved, and the symptoms vary according to the site. One must be constantly on the look-out for this combina-

tion of diseases and be prepared to treat the patient accordingly.

TREATMENT

Control of the polycythemia must be attempted by the various methods available. These include roentgen irradiation and therapy with radioactive phosphorus and acetylphenylhydrazine. The use of the first two should be limited to those with special training. The administration of acetylphenylhydrazine requires care and thought. The dose is 0 1 Gm, and the frequency of administration varies with different patients. Some have required 0.1 Gm. three or four times a week to keep the blood count within normal limits; others need a dose only once in 10 days. Frequent blood counts are essential to regulate the treatment, which is not without some risk of producing profound anemia. Transfusions may rarely be necessary to counteract the effects of overtreatment.

Phlebotomy should be actively used whenever indicated to produce prompt response. It should be remembered that while phlebotomy reduces the total amount of blood it sometimes fails to reduce the cell concentration per cubic centimeter of blood and therefore may have relatively little effect on the thrombosing tendency

Treatment of the thrombosis should be essentially that outlined in Chapter XX For example, thrombosis in the veins of the legs should be treated by warm moist packs and elevation Anticoagulant therapy is indicated, although the use of Dicumarol, Tromexan and heparin in this type of case is more difficult than in the usual case of thrombophlebitis. For some unexplained reason the prothrombin level in these patients is subject to unusual fluctuations under therapy We have treated a number of thrombophlebitic patients with polycythemia. In most, there was no problem, but in some, anticoagulant treatment was exceedingly difficult However, because it may be life-saving, the risks must be taken and the physician should be willing to assume the responsibility in order to preserve the patient's health and even his life.

CHAPTER XXVI Thrombocytic Acroangiothrombosis (Thrombotic Thrombocytopenic Purpura)

THIS SYNDROME was first described by Moschowitz in 1925, and since then about 30 cases have been reported Most of them have not been diagnosed or even suspected until autopsy, and the characteristic findings are outlined here so that the syndrome may be considered in patients exhibiting them The most common and impressive clinical and laboratory findings have been

1. Listlessness and malaise; arthralgia
2. Fever, chronic and persistent.
3. Anemia, severe, out of proportion to known blood loss.
4. Purpura, frequently hematuria, prolonged bleeding time, but usually a normal clotting time.
5. Increased capillary fragility in most cases.
6. Thrombocytopenia
7. Hyperplastic bone marrow.
8. Focal neurologic changes frequently involving the central nervous system and cranial nerves.
9. Hepatosplenomegaly, not universal.
10. Jaundice
11. Frequent association with sensitivity phenomena.

PATHOLOGY

Although the presence of all or a majority of these changes should lead to the suspicion that one is dealing with a case of

thrombocytic acroangiothrombosis, the syndrome cannot be diagnosed at present without the histologic demonstration of widespread and characteristic changes in the walls of the minute vessels with thrombosis.

The initial changes consist of an accumulation of vacuoles, the content of which is not known. Granular material which stains red with leukofuchsin is deposited in the intima and near the internal elastic layer, which subsequently disintegrates. The minute vessel wall, usually of an arteriole, may rupture externally, producing a hemorrhage, or internally, where platelets, endothelial cells and fibroblasts and other components of the blood may form a propagating thrombus along the vessel wall. Local aneurysmal dilatations have been reported. The granular material has no lipid content, but its exact composition is unknown.

Pathogenesis

A simple statement suffices here the pathogenesis is unknown Since the condition rarely has been recognized in life, many studies for infectious agents, bacterial, viral or rickettsial, have been inadequately carried out.

Sensitivity to a variety of agents and drugs has been suggested, but no definitive evidence has been advanced to support this hypothesis.

Treatment

Since the cause and fundamental mechanism of this disease are unknown, therapy can only be palliative

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CHAPTER XXVI · Thrombocytic Acroangiothrombosis (Thrombotic Thrombocytopenic Purpura)

THIS SYNDROME was first described by Moschowitz in 1925, and since then about 30 cases have been reported. Most of them have not been diagnosed or even suspected until autopsy, and the characteristic findings are outlined here so that the syndrome may be considered in patients exhibiting them. The most common and impressive clinical and laboratory findings have been

1. Listlessness and malaise; arthralgia.
2. Fever, chronic and persistent.
3. Anemia, severe, out of proportion to known blood loss.
4. Purpura, frequently hematuria, prolonged bleeding time, but usually a normal clotting time.
5. Increased capillary fragility in most cases.
6. Thrombocytopenia.
7. Hyperplastic bone marrow.
8. Focal neurologic changes frequently involving the central nervous system and cranial nerves.
9. Hepatosplenomegaly, not universal
10. Jaundice.
11. Frequent association with sensitivity phenomena.

PATHOLOGY

Although the presence of all or a majority of these changes should lead to the suspicion that one is dealing with a case of

thrombocytic acroangiothrombosis, the syndrome cannot be diagnosed at present without the histologic demonstration of widespread and characteristic changes in the walls of the minute vessels with thrombosis.

The initial changes consist of an accumulation of vacuoles, the content of which is not known. Granular material which stains red with leukofuchsin is deposited in the intima and near the internal elastic layer, which subsequently disintegrates. The minute vessel wall, usually of an arteriole, may rupture externally, producing a hemorrhage, or internally, where platelets, endothelial cells and fibroblasts and other components of the blood may form a propagating thrombus along the vessel wall. Local aneurysmal dilatations have been reported The granular material has no lipid content, but its exact composition is unknown

PATHOGENESIS

A simple statement suffices here: the pathogenesis is unknown Since the condition rarely has been recognized in life, many studies for infectious agents, bacterial, viral or rickettsial, have been inadequately carried out.

Sensitivity to a variety of agents and drugs has been suggested, but no definitive evidence has been advanced to support this hypothesis

TREATMENT

Since the cause and fundamental mechanism of this disease are unknown, therapy can only be palliative

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CHAPTER XXVII: Lymphedema; Lymphangitis

OF THE THREE major portions of the circulatory system, the lymph system is the least understood. Little was known about the anatomy and physiology of the lymph vessels until Drinker, Field and other workers pieced together a picture which, although incomplete, has provided some understanding of the function of the system and the pathologic processes which result in lymphedema

Lymph vessels are for the most part minute. They possess an unbroken endothelial lining bathed in the tissue fluid which is found outside the blood and capillaries and in cellular interspaces. When there is an abnormal accumulation of this fluid in the soft tissues the result is swelling, called lymphedema. Blood vessels are accompanied by lymph vessels which have valves not unlike those of the veins.

In the legs the lymph vessels are divided into deep and superficial systems, with major communications at the popliteal region and the region of the inguinal lymph nodes. Most of the lymph vessels peripheral to the knee drain into the popliteal lymph nodes, from which a relatively large lymph vessel courses along with the femoral vessels in Hunter's canal, then through the pelvis to end in the external iliac nodes just distal to the bifurcation of the aorta. Many of the lymph vessels of the thigh drain into the inguinal lymph nodes which in turn drain through lymph vessels into the external iliac nodes Deeper lymph vessels in the muscle sheaths of

the thigh drain into the large iliac nodes. In some places lymph trunks are embedded in the adventitia of the walls of blood vessels The superficial and deep vessels of the hands and arms pass up into the axillary nodes, sometimes interrupted by a cubital lymph node, at which point the superficial and deep lymph vessels are connected.

If a large lymph vessel is interrupted, circulation may be carried on by collateral vessels Regeneration of cut lymph vessels is generally rapid, although there are numerous instances in which scar tissue has interfered with regeneration, especially in the region of the major groups of nodes. The interruption of return flow of lymph may then be serious enough to cause lymphedema. This complication not infrequently follows resection of the axillary and inguinal lymph nodes, as, for example, in radical surgery for cancer.

The endothelium of lymph vessels is highly permeable and admits material forced upon its outer surface Lymph is moved along as a result of active and passive contraction of the musculature The rate of flow of lymph is more rapid than is generally realized. For example, trypan blue injected into the lymph vessel of the foot of a dog reaches the receptaculum chyli in 10 seconds. On exposure to air lymph clots more slowly than blood because of deficiency of thromboplastic material which is supplied to a large degree by platelets that are present in the blood but not in lymph Average clotting time by the Lee-White technic is 10–20 minutes

It is interesting that removal of the iliac and inguinal lymph nodes of animals does not lead to edema, whereas in man lymphedema is likely to be a permanent result of surgery which interrupts lymphatic channels. Although frequently thought to be a sequel of complicating infection, this has occurred in patients in whom no evidence of infection was present at the time of or after surgery.

Numerous factors may play a part in the production of lymphedema, but the mechanism of obstruction is essentially the same regardless of etiology. The first step is obstruction, due either to an inflammatory or to an noninflammatory process or by lymphan-

giectasis. With obstruction there is a backing up of lymph, with increase of pressure and dilatation of the lymph vessels peripheral to the point of obstruction. This interferes with proper drainage from the tissues and the lymph pools in the tissue spaces. Nature attempts to find new channels, but there are none constructed to carry away lymph, especially against gravity, and inadequate valves prevent removal of the fluid. The protein content of the lymph increases and fibroblasts proliferate, increasing the amount of fibrosis and causing further obstruction and stasis, so that a vicious cycle is established.

Repeated attacks of an erysipeloid nature often complicate the picture by producing obstruction of the lymph vessels.

I have studied a male patient who has had more than 90 erysipeloid attacks in the past 31 years. Each attack has been characterized by general malaise, high fever, leukocytosis, redness of the leg and increased swelling. He has a severely edematous leg up to the groin at all times and may eventually require a Kondoleon operation, though risky because of the chronic inflammation. Only one leg has been involved.

A late effect of this type of process is thickening of the skin and subcutaneous tissue with replacement of the tela subcutanea and adipose tissue by enlargement of lymph spaces and extensive proliferation of lymphoblasts. Ordinarily this does not affect the muscles, except as the condition limits muscular activity and produces secondary atrophy.

Noninflammatory Lymphedema

Primary lymphedema (precox).—This term is applied to the lymphedema which develops spontaneously early in life, usually in females between 7 and 30. It is most often noted shortly after puberty. The lymphedema may be due to congenital underdevelopment of lymph vessels or to an unexplained obstruction of the lymph nodes or larger lymph vessels at the time of puberty. Unrecognized infection no doubt plays a part in some cases classified in this group.

The disturbance is especially noticeable after the patient has been standing for long periods. It is most pronounced in warm weather. There frequently appears to be an aggravation of the condition about the time of menstruation, probably owing to pelvic congestion and increased back pressure. In most patients, only one extremity is involved in the early stages With the passage of time one or more additional extremities may be affected The condition usually progresses over a period of years, but may develop rapidly and in a few months be severe.

As an extremity (usually a leg) grows progressively larger and looks unsightly it becomes heavy and uncomfortable, but pain is rare. About 15 per cent of patients have recurrent attacks of lymphangitis or cellulitis of an erysipeloid nature. One of the most distressing features of lymphedema is the psychologic effect of the conspicuous swelling. Young women often develop emotional depression of varying degrees of severity because of it One young woman told me that her husband threatened to leave her unless her swollen leg could be cured.

Congenital lymphedema.—Simple congenital lymphedema is found in only one member of a family, whereas hereditary congenital lymphedema (Milroy's disease) affects a number of members of a family One family in our series has four members in whom the condition developed during adolescence without apparent cause, such as inflammatory or obstructive processes Families with many more cases have been reported. In one child, the right wrist was swollen at birth and remained so

The subcutaneous fat is replaced by fibrous tissue and the lymph vessels are greatly dilated Until lymphoblastic proliferation is quite advanced the edema pits slowly on pressure and the size of the extremity can be much reduced by prolonged elevation Details of treatment are discussed later in the chapter.

Secondary lymphedema—This occurs frequently after surgical excision of the nodes or interruption of the large lymph channels. Why it occurs in only a relatively small proportion of pa-

tients is not always understood, but it is undoubtedly related to interruption of the vessels available for the drainage of lymph from the limb. It may occur without evidence of infection, but unrecognized infection may play a role

Lymphedema often follows occlusion of the lymph vessels by metastases or by direct extension of a growth A variety of malignant diseases, including the lymphoblastomas, may be responsible for this syndrome. To mention a few, lymphedema is commonly associated with malignant diseases of the breast, uterus, prostate, bladder and testes and with Hodgkin's disease, or lymphosarcoma. Following surgery for malignancy the extremities may be free from lymphedema for years, then it may appear without explanation and without evidence of recurrence of the growth It may be due to scarring and fibrosis producing obstructive pressure on the lymph channels. Lymphedema also may follow treatment with radium or x-rays. Here again there is a question whether it is produced by the disease for which radiotherapy is given or by fibrosis secondary to irradiation

Inflammatory Lymphedema of Unknown Etiology

Patients with inflammatory lymphedema generally give a history of recurrent attacks of acute cellulitis and lymphangitis, frequently diagnosed as erysipelas or erysipeloid attacks. The attacks are characterized by sudden onset, the relatively severe and generalized reactions which accompany them and the self-limiting character of each attack The involved extremity becomes red and hot, and red streaks are apt to extend out of the area with an erysipeloid appearance. There may be slight elevation of the edge of the inflamed area, but this is not constant. The patient frequently suffers a severe chill and is nauseated, and the temperature may rise to 106 F. (41 1 C). Sometimes the chill and fever appear before the redness is noticeable The fever is likely to subside within three to five days with rest in bed With recurrences the

lymphedema becomes more severe. The attacks apparently represent successive steps in the progression of the disease.

In the United States the condition is usually attributed to streptococci, which are frequently found on culture of the skin, but the similarity of the attacks of inflammatory lymphedema and those sometimes seen with filariasis cannot be overlooked. The differential diagnosis may be extremely difficult

One example is the case of a patient from the Dominican Republic. This woman, 48 years old, had for 24 years had a succession of attacks similar to those just described. She had severe bilateral lymphedema The attacks occurred on an average of twice a month A serious question, repeatedly considered, was whether she was suffering from filariasis or a streptococcus infection Repeated studies failed to reveal filaria, but that is not uncommon Following penicillin and sulfonamide therapy the attacks subsided in a few days, but since this is the typical course without treatment, it was difficult to determine whether the therapy influenced the attacks in any way

Shortly after seeing this patient I observed a young girl in whom severe lymphedema developed after being bitten by a so-called grass flea in Massachusetts The bite was secondarily infected The history was almost identical with that of the first patient. The flea bite may have been merely coincidental.

In the light of present evidence, the etiology of this condition should be regarded as unknown and should not be definitely attributed to streptococci, which seems to be the present trend.

Secondary inflammatory lymphedema.—It is generally accepted that thrombophlebitis may be associated with lymphangitis and that this may be followed by lymphedema. The combination of venous and lymphatic stasis is frequently seen in medical practice The association of dermatophytosis and lymphedema is also striking. A possible explanation for the role of dermatophytosis appears to be that a splitting of the skin permits the secondary invading organisms to gain access to the lymphatic vessels. This is rather clearly demonstrated by acute inflammatory processes with streaks of lymphangitis extending from the infected area. Infec-

tious diseases such as typhoid fever and pneumonia are often complicated by lymphangitis and lymphedema Certain infections spread rapidly through the lymphatics to the regional lymph nodes Noticeable among these are tularemia Cat scratch fever spreads along the lymph channels but seldom breaks down the peripheral groups of lymph nodes

Filariasis

Filariasis formerly had comparatively slight importance in this country. During World War II, however, a large number of soldiers in the filariasis areas of the Pacific were infected with the parasite Filaria bancrofti. Many showed typical temporary swelling and inflammatory reactions. However, it is impressive that very few cases of lymphedema persisted True elephantiasis has been encountered in practically no patients who have returned from the endemic areas. It appears that these patients received too few inoculations by mosquitoes carrying Filaria bancrofti to produce the elephantiasis that is so common among the natives after many years of daily reinoculation by mosquitoes. It does not seem likely that filariasis will become an important problem as a result of the return of these soldiers to the United States

Careful, repeated searches of the blood for evidence of filarias have been notable for their negative results Almost without exception the soldier-patients we examined in Pacific Coast Army hospitals had already lost all evidence of the disease, although in the Southwest Pacific area just one to three months before they had had minor swellings and slight inflammatory reactions

Sporotrichosis

A relatively uncommon disease that involves the lymphatic vessels is produced by infection by the sporotrichum, a fungus which is found widely in native moss, but especially in peat and other mosses commonly used in cultivation Commonly initiated in gardeners or farmers by a puncture wound from a rose thorn or

other sharp object, the primary lesion is a low grade abscess. After a period of weeks a second abscess may form an inch or so proximal to the first, later a third, and so on, proceeding up the extremity along the lymph channels but not localizing in the lymph nodes We have treated a woman with about 50 such lesions extending from her right thumb to the axilla Seven clinicians and two pathologists had failed to make the diagnosis or even to make the special fungus cultures which make the diagnosis easy Diagnosis is vital, for treatment is very satisfactory. Saturated solution of potassium iodide in doses of 5–20 drops to tolerance three times a day is specific and curative.

Lipodystrophy

Lymphedema should be carefully distinguished from lipodystrophy, which is also common among women and has a somewhat similar appearance. There is no pain or inflammation and it is aggravated by standing and warm weather. Lipodystrophy is characterized by generalized obesity, especially over the hips and thighs. Although it is generally painless, in many instances there is deep tenderness on palpation. Cellulitis is not typical of lipodystrophy, nor is pitting on pressure unless there is accompanying edema.

Treatment of Lymphedema

Medical treatment is sufficient in mild cases An affected extremity is elevated to the point where maximal reduction in size is obtained It is frequently necessary for the patient to be in bed with the extremity elevated to a 45 degree angle for as long as 10 days. The objective is to permit maximal emptying of the lymphatic vessels and tissue spaces. With the extremity elevated the fluid tends to migrate toward the areas where the tissues are drained by normally and partially functioning lymphatic channels. Once the size is reduced to the fullest extent possible, the patient should wear a support whenever he is out of bed. This may be a

properly fitted, heavy elastic stocking or a pure rubber roller bandage measuring 3 in. by 15 ft. applied over a lisle stocking The foot of the patient's bed should be elevated at least 12 in and he should always sleep with his bed in this position in order to permit sustained, continuous nightly drainage of the extremity

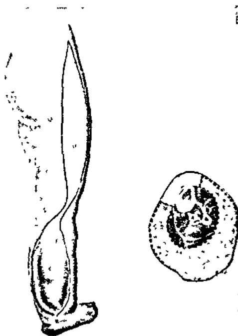
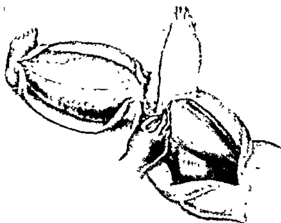


FIG 103—Operation for chronic lymphedema Outline of incision Skin is undermined for 75–100 per cent of leg's circumference, and superficial and deep fascia with outlined skin removed en masse Cross-section shaded area outlined by dots shows section of skin and fascia to be removed (Figures 103–107 from Pratt, G H, and Wright, I S Surgical treatment of chronic lymphedema (elephantiasis), Surg, Gynec & Obst 72 244, Feb 1, 1941)

For patients with pronounced lymphedema or venous edema of the arm the Foley elastic sleeve, which extends from the axillary area down to a half-glove over the hand, is helpful If the fingers are swollen a rubber surgical glove may be worn in addition This



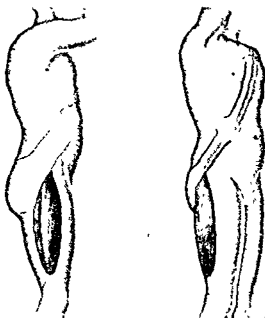


FIG 104 *(above)*—Outlined skin and superficial and deep fascia being removed en masse from two thirds of total area of leg

FIG 105 *(below)*—Broad-based pedicle tube graft being prepared, with base in buttock above area of cutaneous lymphatic blockage.

has helped to reduce edema in many patients, but failures do occur, depending on the process causing the obstruction (see Fig 98)

These measures should be begun as early in the course of the disease as possible and continued indefinitely Some patients show marked improvement, but for many there is no complete cure.

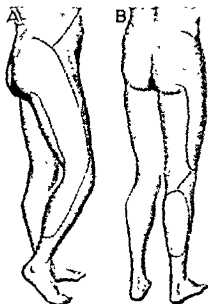


Fig. 106 —*A*, graft in place *B*, after plastic operation to complete leg extension.

The aim of therapy, therefore, is to minimize the degree of swelling This is extremely important, since otherwise edema of disfiguring or even disabling proportions may develop later

The repeated attacks of cellulitis and generalized systemic reactions are treated by rest in bed and such chemotherapeutic and antibiotic agents as seem indicated Continuous sulfonamide therapy prophylactically in severe cases may be worth trying Autogenous vaccines have failed to give satisfactory results

Surgical treatment does not come within the scope of this book

It is worth mentioning, however, that in extreme cases a modified Kondoleon procedure, developed by Ghormley, Pratt and others, sometimes is satisfactory (Figs 103–107) The longest period during which I have observed a patient after this operation is six years, and improvement in the size of the leg was persistent This patient's leg, prior to the surgery, was enormous, measuring 35 in in circumference at the ankle (Fig. 107, *A*) Following operation

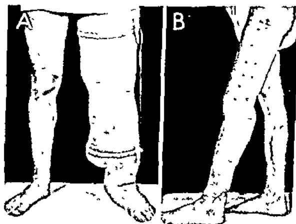


Fig 107—Chronic lymphedema in man, 21 *A*, leg circumference above ankle 35 in before operation *B*, leg three months after operation, circumference 10 in Three years later reduction of leg circumference was maintained despite active daily work

by Dr. Pratt the circumference was reduced to 10 in. and remained so (*B*). In other patients there has been a recurrence of the swelling within five years.

This procedure should be reserved for patients with severe involvement. They should be carefully prepared by prolonged elevation of the leg and administration of sulfonamides or penicillin empirically. The skin is undermined until three fourths of the circumference of the extremity is exposed. The muscle fascia is 100 per cent removed so that the skin can become directly attached to the muscle and hence the lymph can drain through the

muscular lymphatics. This is of great importance. For details regarding surgery, see the reports by Ghormley, Pratt and others

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CHAPTER XXVIII Tumors of the Blood and Lymph Vessels

GLOMUS TUMORS

THE MINUTE arteriovenule shunts known as glomera are subject to nonmalignant growths which have been called glomus tumor, angiosarcoma, perithelioma, painful subcutaneous tubercle, glomangioma, tumor of the myoneural-arterial junction, subungual tumor and angioneuromyoma. Masson and Barré first described this pathologic entity in 1924.

The cause of glomus tumors is unknown. They may follow injury to the area in which they are found, but ordinarily no significant history is available Most of the subungual and finger tumors reported have been in females Rarely, the growth is multiple

PATHOLOGY

The tumors are seen in vivo as minute, bluish, subcutaneous points. They seldom elevate the skin. They are most frequently found under the nail and appear through the nail as a slate-gray spot (Fig 108). They may occur in many parts of the body, superficial and deep. The linings of joints are occasionally involved When resected they are firm and encapsulated and richly supplied with minute blood vessels.

Microscopically the tumor consists of a fibrous capsule filled with masses of "glomus cells" and vascular spaces (Figs. 109 and 110). Under high power magnification the vessels are found to

be lined with a single layer of endothelial cells with a surrounding fibrous layer. Irregularly arranged around the vessels are masses of cuboid or rounded tumor cells which Masson described as epithelioid. Mixed with these cells are smooth muscle fibers, either well developed or in embryonal form Masson believed that the afferent vessels have more orderly muscular coats than the other vessels in the tumor.

The glomus cells are large and have well defined outlines, each with a large central nucleus The cytoplasm is pale and often vac-

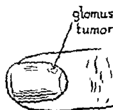


Fig 108 —Common site of glomus tumors

uolated. Some cells contain short smooth muscle fibers in the cytoplasm Mitotic figures are occasionally seen The collagen fibers which form a meshwork between the tumor cells are continuous with the tissue stroma which separates parts of the mass Bundles of myelinated nerves enter the tumor with the afferent artery and are distributed without myelin sheaths among the masses of glomus cells (Fig 111) The fibers usually terminate in end-plates in the stroma and in the cytoplasm of the tumor cells (Fig 112)

The large collecting venule is made up of single-walled endothelium usually with rather swollen, closely placed cells The lumen is crossed with valves and may be subdivided by septums (Fig 113).

SYMPTOMATOLOGY

The discolored mass may be present for some time and, unless traumatized, cause no discomfort Pain, the outstanding symptom,



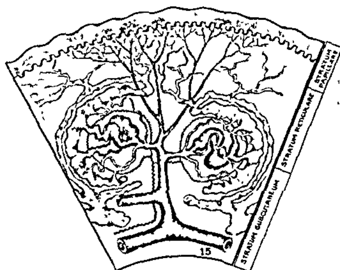


FIG 109 *(above)* —Encapsulated glomus tumor showing vascular spaces and masses of tumor cells

FIG 110 *(below)* —Diagram of structure of glomera from which glomus tumors develop (From Popoff, N. W · Arch Path 18 295, September, 1931; reproduced by permission)

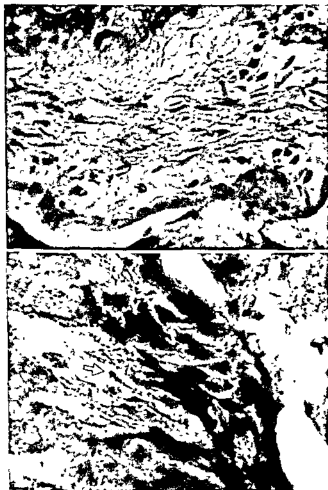


FIG. 111 *(above)*.—Nerve fibers running between groups of glomus tumor cells In lower part of section are vessels outlined by swollen endothelial cells

FIG 112 *(below)*.—High power magnification showing nerve end plate adjacent to glomus tumor cells

is exquisite and severely aggravated by pressure on the tumor. Occasionally it is not present. If the tumor is in a finger the pain usually radiates upward, frequently to the shoulder and neck. Paroxysms of distress may occur without trauma and last for minutes or hours They may be initiated by changes in temperature



FIG 113—Glomus tumor sinus with valves and septums dividing it

and especially by cold. The tumor is usually 3–5 mm. in diameter, one of 3 cm. has been reported Vasoconstriction or sometimes vasodilatation of even major vessels of the extremity is often associated with the attacks of pain Horner's syndrome occasionally occurs on the affected side when the lesion is in the upper extremity. Burning, warmth and sweating of the upper extremity and half of the face on the affected side have been reported.

Subungual tumors are in general more painful than subcutaneous ones. The symptoms usually become progressively more severe.

DIAGNOSIS

The history of agonizing pain and the presence of a minute, nonelevated mass, frequently reddish or bluish, are usually sufficient to make the diagnosis Pain and tenderness are not invariably present Microscopic demonstration of the process is necessary to confirm it. Reflex changes in the vascular bed associated with the pain, such as vasoconstriction as demonstrated by reduced oscillometric readings, lower temperatures or increased sweating on the affected side may accompany the lesion.

Superficially the tumor most nearly resembles the slate-gray mark left by puncture of the skin with a lead pencil The latter represents a form of tattooing and is not permanently painful Such a wound must be borne in mind in differential diagnosis of lesions of the hand, although I have seen lead pencil marks also on the skin of the face and trunk. Other conditions from which these tumors must be differentiated are. (1) hemangiomas, which are usually more red, more superficial and painless, (2) fibrous tumors of the skin, which are more elevated, not tender and less vascular; (3) neoplastic skin tumors, (4) exostoses of the bone, which cause pain, tenderness and localized swelling but are easily identified by x-ray, (5) melanomas, with their black pigment, (6) neuromas without muscle or vascular elements; (7) sarcomas of the blood vessels, (8) subungual papillomas, which are not discolored; (9) subungual corns, which are usually very painful but not discolored, (10) subungual enchondromas, which are usually multiple; (11) subungual angioteratomas, which grow rapidly and are radiosensitive, (12) Boeck's sarcoid

TREATMENT

The only successful treatment is complete surgical excision, Adair described the procedure in a report of 10 cases in 1934 In many cases the nail has been curetted away and the tumor exposed, with severe aggravation of symptoms Because of the mi-

nute size of the mass, careful dissection is necessary. Local anesthesia of the finger is dangerous owing to the high degree of vascular spasm, so risk of gangrene following removal should be avoided by use of a general anesthetic Complete relief of symptoms follows correct surgery. Histologic studies should always be made of the tumor to verify the diagnosis.

Since nothing is known of the etiology and aggravating factors, no advice can be given the patient regarding the prevention of development of more tumors, but multiple tumors are rare. Recurrence of the excised tumor is unlikely if it is completely removed

Two illustrative cases follow.

Case 1—This represents the more common type of glomus tumor The 44 year old wife of a physician complained of agonizing pain and tenderness involving the right fourth finger of four years' duration The pain was so severe that she had been unable to do her housework and spent most of her time protecting her hand from any form of injury. She had seen 22 physicians, most of whom had diagnosed arthritic or rheumatic involvement. Among various other conditions suggested were peripheral neuritis, gout and tumor of the bone She had also been classified as an extreme psychoneurotic, and one physician had *suggested amputation of the finger for relief of the pain*

Careful questioning and examination disclosed that the source of pain was the nail area and that pressure on the nail caused radiation of excruciating pain up to the neck This is characteristic of subungual glomus tumors Close search revealed a small, slate-blue spot about 2–3 mm. in size under the nail at the level of the nail fold where it was somewhat difficult to see Pressure with the tip of a pencil on other parts of the nail did not cause a severe reaction, but pressure on the spot caused the patient to withdraw her hand violently and to cry Pain radiated from that tiny point up into the neck A complete triangular excision of the area down to the periosteum of the bone gave immediate relief The next day the patient was free from pain. The soreness of the excision persisted for a few days, but since then she has had no discomfort

Case 2.—This case represents an unusual manifestation of glomus tumor While in the Army I was asked to review the case of a soldier

with a diagnosis of psychoneurosis for which he was about to be separated from the service. His complaints were of extreme tenderness and pain in the right popliteal space that kept him from drilling or taking other physical exercise involving the use of his legs.

Examination failed to reveal any abnormality, and for this reason he had been classified as a psychoneurotic. With the tip of a pencil, however, one tender point was found from which pain radiated with extreme severity. A diagnosis of possible glomus tumor in the popliteal area was therefore made. An exploratory operation disclosed a glomus tumor about 1 cm. in diameter, about 2 cm. below the surface of the skin, and the diagnosis was confirmed by histologic study. The patient was completely free from the severe pain within 24 hours. He made what appeared to be an uneventful recovery within six days and was returned to duty.

Three months later he was again seen, complaining of essentially the same excruciating pain in the same general area. Although the first glomus tumor had apparently been removed completely and the entire capsule was enclosed in the pathologic specimen, a second glomus tumor was suspected. This would be an exceptional occurrence. Because of the severity of the symptoms, a second surgical exploration was undertaken and a second glomus tumor, this time about 0.5 cm. in size, was found and removed. This diagnosis also was established by microscopic examination.

One month later the patient returned with the same symptoms, and had two glomus tumors not been proved pathologically, the diagnosis of psychoneurosis would have been more seriously entertained. However, again an exploratory operation was performed and a third glomus tumor was removed. Two more glomus tumors were removed from this patient within the next three months—all in the same popliteal area.

This is a rare and remarkable case, but does illustrate the possibility of multiple tumors. In general, multiple glomus tumors, when present, do not occur in such close proximity to each other, and seldom are glomus tumors in parts of the body other than the nail bed as tender and painful as those of this patient. Occasionally, however, excruciatingly painful glomus tumors are encountered in the lining of joint cavities, and in the event of extreme tenderness in a joint cavity the possibility of a glomus tumor must be considered.

Telangiectasia (Hemangioma Simplex; Vascular Nevus)

Telangiectasia occurs in many dermatologic syndromes, including xeroderma pigmentosa, acne rosacea and lupus erythematosus, on simple exposure of the face to wind and sun and on exposure of a portion of the skin to radium or x-rays. Four types of local importance are recognized

Spider nevus araneus.—This lesion arises from a small, pinpoint to pinhead size, red spot with fine vessels radiating in many directions, hence the term "spider" nevus. The lesions are usually multiple and may be found on many parts of the body They are common in the skin of the face, along the lower anterior margin of the ribs and in the thighs, especially of women Most of them occur without explanation An increase in number associated with liver disease is frequently observed Occasionally they are attributed by the patient to insect bites, but this cause is questionable.

Spider nevi are often confused with petechiae, but pressure with a glass slide will demonstrate that they fade easily whereas petechiae do not.

Ordinarily they are of such slight significance that no therapy is indicated If because of the large numbers or increased size the patient wishes to have some of them removed, this may be done by injection of a sclerosing fluid such as sodium morrhuate in minute quantities (0 1–0 3 cc) directly into the central point of the nevus with a 26 gauge needle The use of a fine application of an electrocautery needle to the central vessel is also satisfactory

Senile ectasia (senile vascular nevus).—These are slightly raised lesions, usually seen in elderly or middle-aged persons They represent marked dilatations of minute vessels of the skin. They may appear anywhere on the body, but the anterior surface of the trunk is the usual location. They are purplish or red and range in size from 1 to 10 mm. They have slight clinical significance and require no treatment unless for cosmetic reasons, in which case fulguration is the treatment of choice.

Hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome).—This syndrome is characterized by familial incidence and the development of small multiple telangiectatic lesions of the skin and mucous membranes. There is a strong tendency to hemorrhage from the mucous membranes Many females with the disease have intermenstrual bleeding and frequent epistaxis

A patient was referred to us with a diagnosis of multiple petechial spots on the skin of her hands and fingers (this is a common site of hemorrhagic telangiectasia) For this reason she was being carefully observed for possible subacute bacterial endocarditis. On superficial examination the lesions did appear very much like petechial spots, but pressure with a glass slide caused blanching and careful inquiry confirmed the diagnosis There was a family history of a similar type of lesion and also of frequent epistaxis and intermenstrual bleeding. As is usual in this condition, there was no defect in any of the clotting factors in the blood

Occasionally no family history can be obtained because the condition may skip a generation.

Electrocoagulation, radium therapy and application of chromic acid and other caustics have been used in treatment of the lesions It has been reported that blood transfusions have been necessary to combat the severe anemia resulting from frequent bleeding I have not encountered a case serious enough to require transfusions.

Pulsating telangiectasia (pulsating hemangioma)—This relatively uncommon condition is characterized by elevated red or purplish lesions from 2 to 5 mm in diameter which pulsate quite noticeably. Williams and Snell pointed out that the syndrome is frequently associated with hepatic disease, and it has also been noted with pregnancy and lymphosarcoma

HEMANGIOMA

Ewing defined hemangioma as a benign tumor composed of *newly formed* blood vessels, thus differing from hypertrophy or dilatation of blood vessels already existing In general, hemangio-

mas grow slowly and do not metastasize. More than 70 per cent of hemangiomas are present at birth, and more than 85 per cent have appeared before the end of the first year. These are considered congenital and probably are due to development of embryonic islands of mesodermal tissue. There is strong tendency to growth into connecting canals, which become solid cords of cells They are usually connected with nearby normal blood vessels by efferent and afferent vessels. There are several clinical and pathologic types of hemangiomas

Nevus vinosus (port-wine stain, birthmark).—This is one of the commonest forms. It is a circumscribed or diffuse dilatation and new growth of cutaneous capillaries and venules. The overlying skin is usually thin and so reveals a dark purplish spot. It is usually congenital It is said that about one third of the children born have a small nevus vinosus of the occipital region. Many disappear as the child grows older, but they may extend to involve other areas of the body.

Plexiform angioma (capillary hemangioma, strawberry nevus).—This is a new growth of dilated arterioles, capillaries and veins which results in a definite enlargement and tumor of the subcutaneous tissue and either flat or warty projections of the skin They may be extensive. The color is usually bright red or purple It is difficult to blanch them on pressure These too are considered congenital. It is not uncommon to find them in mixed connective tissue tumors such as hemangiolipomas and hemangiofibromas, and occasionally they are seen mixed, as capillary hemangiolymphangiomas.

Cavernous hemangioma (nevus cavernosus; cavernoma)—When the vascular channels are highly dilated and the tissue septums become thin, hemangiomas are called cavernous. Almost any organ and tissue may be involved and there are often multiple hemangiomas. *If superficial, they are dark and may be flat or elevated,* circumscribed or diffuse and may be warty in appearance.

They may be erectile and pulsating. When close to the skin the tumors are seen as bluish, soft nodules not unlike dilated veins Frequently they collapse on elevation of an involved limb Thrombosis and calcified phleboliths may occur.

The growths may appear at any age and may be circumscribed or extend slowly to large dimensions, involving an entire limb or



FIG 114—Fluctuant mass which appeared in supraclavicular area after the patient fell off his tricycle It was thought to be due to rupture of the thoracic duct, a hemangioma or a hematocele and proved to be the last Two tappings with a simple size 18 needle and syringe resulted in complete recovery (From Medichrome Series MM—Vascular Diseases, by I S Wright and W T Foley)

organ In the aged, large numbers of small hemangiomas may be seen (Fig 115)

Metastasizing cavernous or cellular angiomas may be malignant and cause death from internal hemorrhage or anemia

Common locations are the face, neck, extremities, liver, bone, stomach and intestines. I have seen several in the area of the buttocks

One case, previously mentioned, was confusing because the patient some months before had fallen heavily on a pile of cracked rock, landing on the buttocks This injury had given rise to an arteriovenous fistula which clinically resembled a cavernous hemangioma until auscul-

tation revealed a loud double bruit, which clarified the diagnosis of a fistula * The diagnosis was confirmed at operation

Diffuse hemangioma is a closely related tumor. It has similar structure and may involve an entire limb Both tumors consist of markedly dilated blood sinuses which appear to represent thin



Fig 115 —Cavernous hemangiomas involving left side of trunk and left arm Seven years previously this patient began having jacksonian epileptic seizures believed to be due to similar hemangiomas in the left cortical area of the brain (From Medichrome Series MM—Vascular Diseases, by I S Wright and W T Foley)

walls of veins It is frequently necessary to differentiate them from multiple arteriovenous fistulas, in which case search for bruits and increased oxygen content of the blood in the sinuses may clarify the picture However, several cases have been seen in which both conditions were present In older patients x-ray study may reveal

* Rarely, malignant cavernous hemangiomas erode both arteries and veins to produce anastomoses with a double bruit.

calcification in the form of phleboliths scattered throughout the tumor; thrombosis is not uncommon.

Racemose or cirsoid hemangioma.—This lesion is a dilatation and complex intertwining of altered and newly formed vessels of small caliber with subsequent involvement of normal vessels It is often seen on the head in connection with the large carotid artery Virchow compared the lesion to a mass of pulsating earthworms It begins externally, extends over the neck and scalp, erodes the skull, penetrates the cranium and may involve the cerebral or meningeal vessels. A variety of pathologic changes may be seen, including fatty degeneration and hypertrophy of any or all of the coats of the blood vessels involved

TREATMENT

The treatment of hemangiomas is frequently unsatisfactory but is worth attempting because of the occasional good result. Some show spontaneous involution, but these are relatively rare The most effective procedures are radium therapy, surgical excision, electrocoagulation and injection of sclerosing solutions These require the skill and equipment of specialists, therefore the details will not be discussed

ENDOTHELIOMA

This tumor may arise from the living cells of the blood and lymph vessels as well as from cells elsewhere in the body Hemangioendothelioma may include, according to Ewing (1) the doubtful endothelioma of corpus cavernosum, (2) Mark-Wald's multiple endothelioma of the bone, (3) a slowly growing tumor of the skin in which a moderate number of blood vessels are lined by many layers of endothelium, (4) an intravascular endothelioma arising in hemorrhoidal and other dilated veins; (5) fibrocellular tumors of the thyroid and ovaries in which the vessels are too scanty and the cells too numerous for angioma and many endothelial cells have become disseminated from the vessel

The treatment of these tumors—surgery, x-ray and radium therapy—is highly technical and should be left to specialists.

Perithelioma

This tumor arises from epithelial cells and is a specific variety of angiosarcoma Although originating from blood vessels, it differs in structure from both angioma and endothelioma These tumors arise in the subcutaneous tissue, especially around the anus, in the orbit, axilla and popliteal space, but not the more exposed regions They are also found in the pia mater, bones, breast, ovaries, kidneys and carotid glands. Treatment, including surgery, x-rays and radium, is highly specialized

Kaposi's Sarcoma

This rare condition, described by Kaposi in 1897, has distinctive clinical and pathologic features Various possible etiologic agents have been considered, including infectious agents, trauma, exposure to cold and fungi, but there is no definite evidence that any of these is significant. It is seen more frequently in Russia, Poland and northern Italy than elsewhere, but is not limited to members of any race Ninety per cent of the cases have occurred in males and generally in older people.

The first change is in the form of hemorrhages under the skin at various depths This is followed by dilatation of blood vessels and deposition of hemosiderin The next step is infiltration into the layers of the skin, the predominating cells being the so-called lymphocytoid cells of Marchand Following this are extensive proliferation of vascular endothelium, formation of new minute vessels and infiltration by lymphocytes and plasma cells Spindle-like cells are found. In a late stage a definite nodular sarcomatous appearance may be noted, associated with numerous mitotic figures.

The lesions are most common in the hands and feet, but may

be found elsewhere. They begin as small, discrete, bluish-red or reddish-brown, flat nodules Thrombosis may be noted in the superficial veins. Metastasis is common to any organ of the body, especially the liver, lungs, gastrointestinal tract and lymph nodes. The prognosis is serious, death usually occurring in one to 10 years Treatment may prolong life but does not save it.

Lymphangioma

This is a tumor arising from and composed of lymph vessels, therefore composed principally of endothelial cells and connective tissue The group includes a variety of slowly growing, usually congenital, single or multiple growths of the skin, subcutaneous and deep tissues and muscles of the neck, trunk, lips, tongue, eye, orbit and mediastinal and retroperitoneal regions They were subdivided by Ewing into lymphangioma simplex, an anastomosing network of spaces and vessels of small and medium caliber, lymphangioma cavernosum, a system of lymph spaces supported by thin walls and septums, and lymphangioma cystoides, a collection of large and small masses of lymph tissue

Lymphangioma cavernosa.—These tumors usually appear at birth or shortly after and grow rather slowly. They are considered congenital. Occasionally they become very large and may involve an entire extremity Most of these tumors occur in the skin or subcutaneous tissue. Numerous groups of what appear to be deep-seated vesicles are often present Puncture causes drainage of large amounts of clear lymph that may continue a long time Cavernous lymphangiomas of the mucous membranes and tongue may be greatly enlarged and disfiguring. Infection is a common complication of lymphangioma.

Cystic hygroma or lymphangioma cystoides.—These also are congenital. Most of them occur in the neck and grow toward the carotid gland and ear or down to the mediastinum and axillary region The mass is thin-walled, easily compressible and transilluminates well As is true of most of the foregoing tumors, therapy

should be in the hands of experts in the treatment of tumors and malignant diseases X-rays, radium or surgery, or more than one, may be utilized. In general, the results are not very satisfactory

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CHAPTER XXIX

Industrial and Medicolegal Medicine: Its Relation to Peripheral Vascular Disease and Injury

In a highly industrialized country such as the United States it is important to recognize the health significance of industrial accidents and their relation to previously existing disease Problems requiring careful study and considered judgment constantly arise.

All injury of a measurable degree results in some disturbance of the circulation of the blood or lymph systems and frequently of both The seriousness of the disturbance depends on the type, the degree and the site of the injury It is inevitable that if major vessels are involved and the damage is severe, the results will be more serious than those of slight and superficial trauma, the exceptions being the unpredictable development of infection or other complications in the presence of slight injury

The general constitutional and psychosomatic make-up of the patient has particular bearing on the management of injuries This has special significance in vascular disease, since many of the findings are largely subjective and in some instances objective findings cannot be correlated with the patient's complaints We encounter individuals in whom the objective findings are slight and the subjective complaints severe and, less frequently, individuals with clear objective evidence of circulatory impairment but scarcely any subjective symptoms.

The variation in the ability to endure pain from one individual to another and even in the same individual from time to time has been well established. Some types of peripheral vascular syndromes present excellent examples of such variation and, like some instances of low back pain, offer unusual opportunities for malingering. As will be illustrated in the cases included in this chapter, each patient should be subjected to a complete survey of the vascular system in accordance with the technics outlined in Chapter II It must always be borne in mind that a local injury which fails to heal or responds poorly to treatment may be a manifestation of a generalized vascular disease which is not prominent enough to be apparent to a casual examiner

For the most part, a careful physical examination with emphasis on the nervous and vascular systems is sufficient. There are times, however, when elaborate investigations are required to establish a correct diagnosis The following cases are illustrative.

Case 1 —A man caught his right foot in a stamping machine and fell over backward in a distorted position Immediately the foot and leg became swollen, indurated, discolored and painful. The diagnosis was severe laceration, tearing and straining of muscles and ligaments and rupture of the blood vessels of the foot, ankle and calf. During the next few months the signs slowly disappeared, but extreme tenderness involving the entire foot to the ankle remained Satisfactory examination was impossible and could not include palpation because of extreme tenderness of the skin. During the next five years this man was seen by more than 50 physicians who submitted various diagnoses, including malingering, various orthopedic conditions of the foot (not confirmed by x-ray studies), vascular disease (proper examination was never performed) and neuritis.

He was referred by the State Labor Commissioner for a differential diagnosis. At the time of the first examination there was no evidence of vascular disease elsewhere in the body. The appearance of the foot was normal There was no pallor on elevation or rubor on dependence —two cardinal signs of vascular disturbance Palpation was unsatisfactory because of constant wincing and withdrawal of the foot. The posterior tibial arteries were present bilaterally, but the dorsalis pedis

artery of the left (opposite) foot could not be felt. Oscillometric readings showed 0 25 degree excursion over *the arch of the normal foot.* They could not be taken for the injured foot because of protestations of extreme pain and sensitivity. The temperature of both feet was low, that of the toes averaging 24-25 C. (76 F.) X-ray study for bony or arteriosclerotic changes of the legs and feet showed absolutely no abnormality, *not even evidence of disuse atrophy. The following study* was then undertaken and a technic was developed which has been found useful in other cases.

Technic for evaluating pain —The patient was prepared for general anesthesia Control temperatures of the toes were recorded and repeated The average temperature of the toes of both feet was 24-25 C (76 F) Cyclopropane anesthesia was then begun. Immediately on completion of induction, motion of the injured foot was found to be free and in no way limited An oscillometer was applied over the arch, and although the dorsalis pedis could not be palpated the reading was 0.25 degrees In view of the same reading in the opposite foot and inability to palpate the dorsalis pedis of the left foot, it was concluded that the dorsalis pedis arteries were probably bilaterally aberrant Surface temperature readings repeated at this time showed no change Carbon dioxide induction was then undertaken The blood pressure, previously 120/80, [illegible] 180/100 It then began to [illegible] essure *reached its peak,* vaso- [illegible] ting for the fall With vasodilatation the temperature of the feet rose rapidly to an average of 30-31 C (87 F) for the toes. The oscillometric readings for the injured foot reached 0 75 degrees and for the normal foot 0 50 degrees of swing The dorsalis pedis arteries were still not palpable, but with such adequate response at the dilating point it was felt that absence of organic vascular *insufficiency had been established*

The next phase of the experiment dealt with the question of malingering The anesthesia was lightened slowly, the test being made for response to pain by pressure on the supraorbital nerve at the site of the groove At the point where strong pressure elicited a marked pain response evidenced by a restless defensive movement, but while the patient was still unconscious, comparative pressures were made on the two feet Pressure on the normal foot elicited no response, pressure on the involved foot elicited a clearcut pain response, with withdrawal and contraction of the body This convinced us that the patient was not a malingerer and that he had real pain and tenderness, and by elimina-

tion of vascular disease we arrived at the diagnosis of pain of neurogenic origin

While he was still semiconscious it was possible to examine the surface areas carefully and to map out what appeared to be the involved zone This corresponded to the distribution areas of the fifth lumbar and first sacral nerves X-rays taken of the corresponding section of the spine showed the fifth lumbar vertebra displaced anteriorly, with sharpening of the articular border. It appeared, therefore, that malingering, organic vascular disease and peripheral neuritis had been eliminated and that the diagnosis was injury to the lower portion of the spine, in all probability incurred at the time he fell over backward in the distorted position For five years the attention of many physicians had been focused on the localized pain in the foot

Case 2 —This illustrates a similar type of study The patient was struck by an automobile while riding a bicycle He was thrown to the

Several teeth were loosened and his bridgework was bent out of shape The handle of the bicycle struck against his abdomen

At the time I examined him he complained that when the right wrist was placed in the dependent position it swelled markedly, remained stiff and was cold and painful He also complained of pain in the groin, abdomen, chest, neck and face and of pain on urination and with bowel movements The right testicle was extremely tender He also stated that he had severe burning pain in the right forearm and sharp pains in the precordium and that all food upset his stomach

Briefly, the physical examination disclosed no obvious evidences of pathology The patient complained of pain and tenderness wherever his *attention* was focused There were two areas of extreme tenderness which on pressure produced a marked protective reaction the right testicle and the right ankle Complete laboratory and x-ray studies also failed to disclose a pathologic process

The test for evaluation of pain (p 513) was therefore undertaken Cyclopropane anesthesia was administered and then lightened until pressure on the supraorbital nerve or styloid process elicited a definite pain response. At that point no pain response could be elicited by pressure on either the right testicle or the right ankle The patient was allowed to regain consciousness *After two minutes of consciousness,* pressure on the supraorbital nerve elicited a clearcut response The

same amount of pressure on the right testicle and the right ankle elicited none After five minutes his reactions to pressure in these areas returned.

The impression was that the problem was largely psychogenic He did not have organic vascular or other organic disease so far as it could be determined and I recommended rehabilitation, occupational therapy and psychiatric treatment The probable diagnosis was conversion hysteria The patient then left the hospital, and instead of having psychiatric treatment went to a surgeon who, taking his complaints at face value, operated on both testicles. The pathologist of the hospital in which the operations were performed reported "no evidence of pathology in the tissue submitted." The patient was returned to me by the Industrial Commissioner with all symptoms greatly exaggerated

Another test for pain response was then performed with the same results, except that this time it was 10 minutes after consciousness was regained before pain response was obtained by pressure on the right testicle The impression was the same as it was on his previous admission except that the situation was exaggerated by surgery which had focused attention on the male genital area Careful study by a competent neuropsychiatrist confirmed the impression The recommendation was made for (1) psychiatric therapy, (2) occupational therapy and (3) a lump sum settlement.

This test for the evaluation of pain, which I first described some years ago, may well be put to more widespread use in the study of cases of this general type.

Injuries Involving Arteries, Veins and Lymph Vessels

Cutting injuries—With cutting injuries one or more blood or lymph vessels may be partially or completely severed The immediate problem is hemorrhage. After the hemorrhage is stopped, serious considerations are whether the vessels can be re-opened and whether the extremity will suffer as a result of circulatory impairment due to thrombosis or complete occlusion of the arteries, veins or lymph vessels. An important related question is whether severed nerves in the injured area may complicate the picture later. Arteriovenous anastomoses are not uncommon following cutting wounds

A metal worker, aged 46, was cutting sheets of Allegheny metal with shears when the metal coiled back, cutting the dorsum of the right forearm just above the wrist. Tendons, nerves, veins and a few small arteries were sharply severed. The surgeon sutured the nerves and tendons and ligated vessels that were bleeding profusely.

I saw the patient about a year later, when he complained of marked enlargement of the right hand, forearm and arm, especially after dependency. There was extreme dilatation of all the superficial veins of the entire extremity, and the engorgement extended over the pectoral area A double bruit extending throughout the heart cycle was clearly heard at the site of the injury The right hand and arm had become definitely weaker than the left although the patient was fundamentally right-handed and the right arm had formerly been extremely strong *When the hand was held below the heart level it became practically* useless because it would swell like a balloon in three to five minutes Oxygen saturation studies showed the oxygen content of the venous blood to be nearly equal that of the arterial blood and much greater than that of the venous blood of the left arm This was clearly demonstrable even without elaborate laboratory procedures, for in the test tubes containing blood taken from the veins of each arm, the blood from the right arm was much brighter red than that from the left arm

Arteriographic studies showed a network of arteriovenous anastomoses at the site of the injury so complex that the vascular surgeons hesitated to attempt surgery. The surface temperature of the right hand and arm averaged 3 degrees (C) higher than the corresponding areas of the left arm Despite the potential difficulties, if cardiac enlargement—a common complication of arteriovenous anastomoses—should occur, an attempt at elimination of the arteriovenous anastomoses or even amputation of the extremity may be necessary.

This is an example of a clearcut injury and subsequent disability There is no question that this patient is entitled to total disability compensation because he is unable to carry on his usual occupation or any work for which he is trained

Penetrating wounds.—These are common causes of arteriovenous anastomoses. Hundreds of such instances were seen during the war and they are not uncommon in industry and even in nonindustrial pursuits in civilian life. One of the more interesting cases I have seen was in a child.

While the child was running along a street, a pair of scissors fell from the window of the third floor of an apartment house The blades were open, and one stabbed the popliteal space The blade was withdrawn, and despite considerable temporary bleeding the wound healed fairly promptly. A month later the involved leg began to increase in size The veins became engorged and swelling appeared in the popliteal space A bruit was heard over the area and the diagnosis was obvious Surgical excision of the fistula and, if necessary, of the adjoining segments of the popliteal veins and artery was advised Because of a great tendency for collateral circulation to develop in the area of arteriovenous anastomoses, circulatory insufficiency seldom occurs after this operation

Crushing injuries.—Arteriovenous anastomoses may result from a crushing injury.

For example, a man fell on a pile of crushed rock from a height of about 12 ft. He landed sitting down Both buttocks were bruised. Nothing more was thought of the incident until several months later, when it was noted that the right buttock was becoming much larger than the left The diagnosis was tumor of undetermined type. When I examined the patient a loud double (to-and-fro) bruit could be heard over the entire right buttock. My diagnosis was arteriovenous anastomoses due to a crushing injury which had produced a fistula between an artery and vein in the buttock area. Surgical excision of the fistula was recommended The operation confirmed the diagnosis

Details regarding the differential diagnosis of arteriovenous anastomoses are given in Chapter XII.

Straining or tearing of the vascular tree.—Such injury may occur in a wide variety of circumstances It frequently results from a blow by a heavy object, as by an automobile. As the victim falls, the leg may be twisted into an awkward position, producing sudden, severe torsion on the extremity and the body as a whole This kind of accident is usually associated with other serious immediate damage, including severe subcutaneous hemorrhage of the injured part Free hemorrhage does not occur unless the skin is broken Secondary vascular complications may include thrombosis of an artery or vein, aneurysm, phlebitis, arteritis, edema on a venous or lymphatic basis and occasionally an abscess or liquefying clot

Arteriovenous anastomoses are not very common in this type of injury. The following case is illustrative.

A man aged 56 was crossing the street when he was struck behind the knees by the bumper of an automobile. There were considerable strain and bruising, but apparently no serious injury. About a year later a pulsating mass appeared behind the right knee and gradually increased in size. During the next several years the mass became larger, but the patient would not permit treatment. About six years after the accident a sudden pain occurred in the right foot. The entire foot became cyanotic and the tips of three toes became gangrenous. There were extreme pain and tenderness in the lower leg, which became swollen. It appeared that amputation was inevitable.

The diagnosis was popliteal aneurysm and the patient was admitted

[illegible]

Pressure caused by the swelling complicated the picture. Exploration revealed the popliteal (tibial) nerve stretched tightly over the bulging mass, which turned out to be a firm clot walled in by the popliteal structures. In other words, a false aneurysm had been formed. The entire posterior wall of the popliteal artery was eroded for over an inch. A Matas obliterative procedure was performed.

The tip of the gangrenous fifth toe was amputated, and the patient never had pain in his foot thereafter. He was kept on a Sanders oscillating bed and the foot was put under a thermostatically controlled cradle at 96 F. Recovery was uneventful. At the time of operation a small aneurysm of the opposite popliteal artery was noted. It was decided to keep this under observation rather than to operate then.

Arteriosclerosis may well have played a part in the preparation of the arterial wall for the aneurysms. In view of the frequency with which aneurysms are precipitated by injury it seemed likely that in this case the injury had been at least an aggravating factor. Against this hypothesis is the fact that a year elapsed between the accident and recognition of the aneurysm. In addition, there is the fact that the process is bilateral.

Another case illustrating the effects of injury follows.

A man aged 32 was lifting a heavy box which slipped and fell back

against his legs, producing a severe strain on the muscles and soft tissues Following recovery from a bruise, phlebitis of the left saphenous vein developed This spread to involve the peripheral branches and also proximally to involve the femoral vein and veins of the trunk Two pulmonary and one renal emboli were known to have occurred, but after 18 months the process quieted down and recovery took place The after-effects are venous edema with a tendency to varicosities of the saphenous tree.

Similar cases have been seen following such accidents as sprained ankle and twisted knee.

Mechanical or chemical erosion —This may either initiate vascular pathology or aggravate an existing vascular disease

Case 1 —A 32 year old laborer had a job carrying bundles of chipped slate shingles. The chips were sharp and ultimately wore down the skin of the finger-tips, producing ulceration When first seen there was an angry, infected erosion of the tip of the right fifth finger He was a heavy smoker The process suggested thromboangiitis obliterans Arteriographic studies verified the presence of a process resembling thromboangiitis, with peripheral obliteration beginning in the smaller arterial and venous radicles and extending centrally to involve the palmar arch The erosion was an aggravating factor superimposed on an early or latent case of thromboangiitis obliterans

Case 2 —A man aged 55 had been occupied for many years as a copier of music The work necessitated the use of black ink Strong pressure against certain areas of the fingers was incidental to grasping of the pen Three or four times a day an ink eradicator was used on the same areas to remove ink stains Gradually ulcerations began to appear at exactly the areas involved by pressure, ink and ink eradicator, namely, the tips of the first and second fingers and the approximating surface of the third finger at the level of the distal phalangeal joint Evidence of arterial thrombosis developed The process involved the palmar arch, then the radial artery, and despite the use of vasodilators, including typhoid vaccine, abstinence from tobacco and other therapy, the thrombus, now easily palpable, steadily ascended the arm into the brachial artery

When after three months the thrombus reached a point about 3 in below the axilla it was felt that a radical procedure was essential An operation was performed by Dr Robert Ackerly, who removed a proximal segment of the brachial artery A thrombus about 10 in long

extending into the axillary artery was loosened and removed and th artery was ligated proximally. The patient recovered satisfactorily. Si months later there had been no extension of the process and the arr functioned fairly well. Sections of the artery showed changes abou which the pathologists hesitated to commit themselves The pathologi process was similar to thromboangiitis obliterans. The history and onse were not typical Again one cannot be certain that the condition starte in a normal vascular tree The irritating factors no doubt either pre cipitated or aggravated the active pathologic process

PRIMARY AXILLARY VENOUS THROMBOSIS

This is not an uncommon occupational disease. The followin case is a notable example

A man aged 32 worked in a printing establishment where he was obliged to lift bundles of large sheets of paper weighing 40-70 lb and swing them across to a second pile. While at work a co-worker asked "What is wrong with your right hand? It is bigger than your left one." The patient examined it and realized for the first time that the entire right extremity was larger than the left one and was stiff. The next day the swelling was greater, there was pain, and a large thrombotic mass was seen in the axillary vein Superficial veins became dilated in an attempt at compensation and increased steadily in size. This was especially noticeable over the biceps, deltoid and pectoralis areas Months of rest resulted in slow canalization of the thrombus, but four years later there were still stiffness, weakness and marked compensatory dilatation of the collateral veins of the arms, shoulders and chest The patient was unable to do any physical work requiring use of his arm

In most instances axillary thrombosis does not result from a single serious injury, being more apt to follow constant repetition of a type of motion and strain which traumatizes the axillary vein and encourages thrombosis This may be due in some cases to pinching of the subclavian axillary vein by the structures of the shoulder girdle, e.g, between the clavicle and the first rib. It is important to realize that, although these patients may recover sufficiently to be free from discomfort and edema, any occupation requiring activity resembling that of the original one is very apt to precipitate a recurrence of the syndrome.

This was exemplified in a laborer who worked with a shovel (previously mentioned on p. 449). An attempt was made to rehabilitate him by teaching him to upholster the seats of automobiles. It was thought that this would be sufficient change from his original occupation of shoveling to permit satisfactory rehabilitation. However, the muscular action of stretching the material over the automobile seat apparently traumatized the axillary vein and there was prompt recurrence of the axillary thrombosis.

For the most part these patients must be re-trained for completely sedentary occupations that do not require further insult to the involved part if they are to be rehabilitated.

PRESSURE OCCLUSION OF ARTERIAL CIRCULATION

Pressure on an artery must also be considered an important complicating factor following trauma.

For example, a man suffered a simple fracture of the tibia and fibula just above the ankle A cast was applied. The next day his physician noted that the foot was discolored and removed the cast. The dorsalis pedis artery could not be palpated at first and the foot felt cold, but after a while the color and warmth returned and pulsation could be felt. The cast was reapplied and the patient allowed to go home. The next day the patient was suffering from severe pain and was admitted to the hospital, where the cast was removed The leg was found to be markedly discolored and cold and no pulsation could be felt above the popliteal artery This observation was verified by oscillometric readings. Blebs began to form and the temperature rose to 103.5 F He was very septic, since all vasodilators were ineffective and high amputation appeared to be the only recourse to save his life. Histologic study showed no definite thrombosis of the artery, the damage having apparently been done by pressure of the cast on the popliteal artery and the collateral vessels of the popliteal space Necrosis of the soft tissues was evident throughout the leg The patient's life was saved, but at a high cost.

TRAUMATIC VASOSPASTIC DISEASE (PNEUMATIC HAMMER DISEASE) AND RAYNAUD'S SYNDROME

For the development of traumatic vasospastic disease, two conditions appear to be necessary. (1) the hand or fingers must be

exposed to repeated, excessive trauma over a period of years, and (2) the individual must have a neurocirculatory make-up which makes him susceptible. The disease is usually ascribed to the use of apparatus with high vibration rates (2,000–4,000 strokes per minute) such as a pneumatic hammer or a shoemaker's pounding or lasting machine. I have, however, seen cases in typists, in two concert pianists, a telephone switchboard operator and a handball

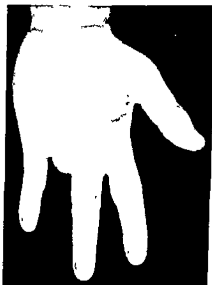


FIG 116—Traumatic vasospastic disease due to a single injury. (From Medichrome Series MM—Vascular Diseases, by I S Wright and W T Foley)

expert, in each of whom a typical vasospastic picture characteristic of Raynaud's syndrome was produced. In each case it was difficult to produce the reaction when the body was warm but was relatively easy in a cool environment. The only treatment was change of occupation. *The concert pianists had to give up their careers.* (See Chapter VI for further discussion.)

Although repeated trauma seems typical of this syndrome, traumatic vasospastic disease may follow a single injury, as in the following cases.

In July, 1945, a man's left hand was injured by an exploding hand grenade. The fourth finger was amputated. Three years later the remaining fingers easily became cold and cyanotic and, in addition, frequently showed evidence of typical attacks of Raynaud's syndrome (Fig 116).

Recently the patient's brother injured his left hand in the accidental firing of a rifle The bullet passed through the palm, no fingers were lost The wound healed, but traumatic vasospasm developed that was quite similar to that in his brother's hand. This either is an extraordinary coincidence or indicates that, in this family, injuries of this type are apt to cause vasospastic phenomena.

THROMBOANGIITIS OBLITERANS

Thromboangiitis obliterans is frequently confused with the late effects of trauma The disease may be present and slowly progressive for many years without symptoms, signs or recognition. This has been demonstrated by careful vascular examination, including arteriography, in extremities previously assumed to be free from any vascular disease. Trauma, even though slight, may initiate a process which progresses from a nonhealing ulcer to local or massive gangrene. The question which presents itself to the doctor concerned with compensation or industrial medicine is whether the injury or underlying thromboangiitis obliterans is responsible for the ultimate condition.

It must be conceded that when the wound progresses without interruption from the time of the injury, the trauma is at least an aggravating factor and as such is compensable under the laws of most states When the wound heals, only to break down later, or there is no evidence of a serious condition until weeks or months after the accident, the problem is more difficult to evaluate A definite relationship does not seem likely if no signs or symptoms whatever are present for approximately three months or more between the time of the accident, or the time of healing of a very minor injury, and the onset of symptoms When symptoms appear in a shorter period the relationship is debatable because thromboangiitis obliterans is a low grade process which may be active for

some time without causing enough discomfort to focus a patient's attention on an involved area. Conclusions in each case must be reached only after careful evaluation of all factors. One should always remember that most males in the susceptible age group (20–50 years) smoke, and the use of tobacco in itself may aggravate or, indeed, initiate the disease. Selected cases may illustrate various aspects of this problem.

Case 1.—A man 42 years old caught his left third finger in an elevator gate. The finger was badly cut. A large thrombus developed in the soft tissues and the physician made a further incision to release the clot. After more than two years the lesion had not healed. Meanwhile, several incisions in other parts of the body had healed rapidly. On the left third finger was a sharply demarcated, dry, painful ulcer that involved most of the surface of the tip.

Oscillometric readings showed marked reduction of oscillations in the left wrist (the affected side). Both radial arteries responded rather sluggishly to the Allen test, and it appeared that the functional capacity of the left ulnar artery was definitely reduced. Study of the circulation of the lower extremities showed lack of pulsation of the dorsalis pedis artery on the right side and of the posterior tibial and dorsalis pedis arteries on the left. The left foot showed 2+ rubor on dependency, 1+ pallor on elevation; the right foot did not show these color changes. The blood sugar content and cell count were within normal limits. Sedimentation rate by the Westergren method showed a 60 mm. drop in one hour.

In view of the generalized evidence of vascular disease, it was believed that this patient had early but fairly widespread thromboangiitis obliterans and that this explained why the lesion of his left finger had failed to heal. Nevertheless, if we accepted his statements that he had no symptoms prior to the accident, that lesions in other parts of his body had healed while the finger remained unhealed, and that his current disability was confined to the lesion of the finger, we must consider [illegible]
ease [illegible]
the [illegible]
injury [illegible]
obliterans. It was recommended that active attempts be initiated to heal the lesion, including total, permanent abstinence from tobacco, admin-

istration of typhoid vaccine and application of warm soaks. The prognosis is good if the patient follows this régime precisely

Case 2—*A man gave the history of having struck his right knee* against a table 15 months before he was seen The knee was moderately painful at the time, but he continued his work During the next night, at work, *the leg pained him severely and he asked to be allowed to go* home He was away from work for the greater part of five or six weeks The knee was swollen the day after the accident and appeared slightly bruised, but there was never an open lesion. The knee was strapped and short wave diathermy treatment given The symptoms disappeared

At the time of his first visit to our clinic 15 months later, his complaints were referred to both feet, especially around the areas of the first toes. The discomfort was of recent origin. His feet felt cold and numb. They developed 2+ rubor on dependency but no marked pallor on elevation. The left dorsalis pedis artery could not be felt The right dorsalis pedis artery and both posterior tibial arteries were palpable. The radial and ulnar arteries were active bilaterally There was a marked diminution of the oscillometric readings for the left leg

It was our impression that this was an early case of thromboangiitis obliterans unrelated to the accident to the knee The reason for this decision was that the symptoms in the injured knee had completely subsided, 15 months later symptoms had developed in the tips of his toes *and there was definite evidence of occlusive vascular disease.* It was felt that he did not have a compensable lesion at the time of the examination

At times, thromboangiitis obliterans figures in malpractice suits

For example, a man aged 29 had what appeared to be a simple paronychial infection around the left first toe The surgeon decided to establish surgical drainage and as a preliminary procedure instituted a procaine block around the base of the toe, using the standard procaine-epinephrine solution After the injection the entire toe promptly turned dead white and never regained normal color The next day it was black and mummification had set in After the anesthesia, and not until then, the surgeon palpated for the dorsalis pedis artery and found it occluded The toe finally demarcated and was amputated The patient was suffering from thromboangiitis obliterans which was undoubtedly present before the operation With the deeper vessels occluded, the injection of epinephrine subcutaneously apparently reduced the potential circulation to a level incompatible with life of the tissues

The lesson in this case is obvious. No surgery, however simple, should be undertaken on the extremities before the status of the peripheral circulation is determined. The surgeon who neglects this precaution lays himself open to malpractice suits

A similar case was seen in which a surgeon lost the second finger of his right hand because of insufficient study of the circulation before a procaine-epinephrine nerve block was established at the base of the finger.

BLOOD DYSCRASIAS

Occasionally hematologic disturbances confuse the picture

For example, a painter slipped and fell down a few steps, striking the right knee, three years before our examination. The knee was scratched at the time of the accident but did not cause appreciable pain The foreman sent him home and the patient painted the wound with iodine. That night the knee began to be warm and uncomfortable and the next morning it was very red and swollen. Three days later, when a physician first saw it, infection was rapidly spreading Shortly thereafter the patient was admitted to a hospital, where he was repeatedly operated on. For some months there was a considerable amount of purulent drainage After about five months he began to work but was unable to continue for more than a few days at a time For three years he repeatedly attempted to work but had been unable to continue

At the time of our examination his leg was definitely swollen He complained of fatigue, extreme nervousness and weakness. After a few hours he would feel unable to continue his work despite the fact that his fellow workers considered him psychoneurotic. This further depressed him. During examination it was noted that the mucous membranes were plethoric. Blood pressure was 132/98. The spleen was palpable but not extremely enlarged. Oscillometric readings were normal and the arterial pulsations could be felt at all normal points. In order [illegible]
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eters [illegible]
evening. There was a slight, certainly not pronounced, increase in size of the legs. The most significant finding was a red blood cell count of 8,400,000 with 21 Gm. of hemoglobin. Further study disclosed typical

polycythemia vera which was not due to the original injury It yielded rather promptly to therapy

This is another example of the importance of reviewing the patient as a whole rather than concentrating exclusively on the history and site of the injury.

ARTERIOSCLEROSIS OBLITERANS

Arteriosclerosis obliterans, like thromboangiitis obliterans, may be present for years before it is recognized. Frequently an open lesion from a major or even a very minor injury will not respond to therapy of any kind. From even the most trivial lesion, serious complications may be anticipated, including nonhealing ulceration, local gangrene, secondary infection, more massive gangrene, possible amputation and, not infrequently, sepsis and death Therefore any lesion in an older person must be cared for with the greatest of detail, and it is essential that an over-all study of the circulation be made in order to evaluate the relationship of the general vascular status to the local lesion.

It must be remembered that sudden occlusion in an arteriosclerotic artery may occur at any time. The individual may be walking down stairs or he may be in bed It is inevitable that a certain percentage of such occlusions will occur while the individual is at work These episodes, which are part of the natural history of the disease, are not considered compensable under present laws Therefore, all details regarding any injury may have legal significance

For example, it was claimed that an arterial occlusion that occurred shortly after a man's foot slipped while he was going up a flight of stairs (although he fell back only one step) was due to that incident. Gangrene of the toes ultimately developed, followed by sepsis and death.

At autopsy the major vessels of the legs and aorta showed profound arteriosclerosis, and all branches of the aorta showed an eccentric thickening of the intima with some narrowing of the lumen. The iliac artery showed advanced atherosclerosis, and the coronary arteries also showed severe atherosclerosis, with almost complete obliteration of the left

coronary and evidence of an attempt at canalization. It seemed likely that the patient had generalized, severe arteriosclerosis obliterans, and the fact that his foot slipped back one step could hardly be considered the cause of his death, although this was claimed in court

SYPHILIS, VASCULAR DISEASE AND TRAUMA

Syphilis may be the underlying disease complicating trauma A gumma may develop in a slightly traumatized area. Syphilitic infection may be responsible for aneurysms thought to be due to injury Frequently an inclusive differential diagnosis is not critically considered as in the following case

A man in his early forties was referred by the Labor Department About six weeks before, during a very cold spell, while driving a bus his foot suddenly slipped off the clutch and he struck his left shin. He *rested for about a week and then returned to work against his physician's* advice Seventeen days after the accident he suddenly felt a sharp pain in his left foot and calf The foot became more painful and the following day several of the toes became gangrenous He was hospitalized. Absence of pulsation of the dorsalis pedis artery was noted, and the diagnosis was trauma or frostbite superimposed on arteriosclerosis obliterans Treatment was conservative Fourteen weeks later, the gangrene was still present although alleged to be improved

Careful observation before the patient was touched revealed an important point, hitherto unrecognized, namely, that the entire left leg and foot moved regularly with each pulse wave. *Palpation of the popliteal* space disclosed a walnut-sized popliteal aneurysm. Further examination revealed a definite aneurysm of the right popliteal artery, aneurysms in both axillary arteries, and evidence of aortic aneurysm, which x-ray examination later confirmed. The logical explanation for absence of dorsalis pedis pulsation and gangrene was that a small portion of clot from the left popliteal aneurysm broke loose and descended the artery to occlude it.

It is improbable that the episode with the clutch or the cold weather affected the course of the disease, since sudden peripheral embolic phenomena frequently take place in the presence of popliteal aneurysm without trauma Syphilitic etiology was considered in view of the patient's age and, especially, other aneurysms. X-rays of the extremities failed to reveal any evidence of arteriosclerosis However, the blood

Wassermann reaction was reported to be negative, and reaction of the spinal fluid was also negative. An operation for obliteration of the popliteal aneurysm was recommended, but this was refused About eight months later an amputation was necessary Detailed study of the aneurysmal tissues gave no clue as to the etiology of the aneurysm It was quite unlikely that the condition was on a syphilitic basis. It probably was due to congenital weakness of the walls of the arteries and a tendency to aneurysmal dilatation in multiple areas It could hardly be considered due to a compensable injury

SYNDROME OF THE SHOULDER GIRDLE

For many years cervical ribs were considered responsible for the syndrome of tingling, numbness and sometimes pallor, trophic changes or even gangrene of the fingers Later, attention was called to the scalenus anticus syndrome The vascular syndrome due to prolonged hyperabduction of the arms, which I originally described, has been encountered in persons obliged to work with their arms in that position Examples have been seen in persons who rivet the under surfaces of airplane wings, paint ceilings, work in repair pits under automobiles and at similar occupations. It is often serious enough to require change of occupation These conditions are discussed at length in Chapter X

THROMBOPHLEBITIS

Pressure per se may be sufficient to produce phlebitis. A typical example is thrombophlebitis in a vein of the dorsum of the foot directly under shoe laces tied so tightly as to produce severe pressure of the vein against the bones of the arch of the foot In one patient aged 34 the result was migratory thrombophlebitis that eventually involved both legs, both arms and hands, the abdominal and spermatic veins and in all probability the coronary sinuses The condition continued for more than 10 months before subsiding.

Thrombophlebitis is frequently initiated and aggravated by injuries, many of which seem insignificant. Why this is so, is diffi-

cult to determine. The following hypothesis has its advocates. The trauma may initiate a reaction in the intima of the vein with local roughness of the intima and increase in thromboplastin (thrombokinase). This may cause adherence of platelets, white cells and later red cells to produce a thrombus. In migratory thrombophlebitis bits of clot, bacteria or viruses apparently break off and settle elsewhere One explanation of why this migration seldom follows arterial injury rests on the direction of blood flow. In the arteries the blood flows peripherally and has limited distribution, whereas in the veins it flows centrally and can have widespread distribution If this theory should be correct, why do we not have multiple arterial involvement with migratory thrombophlebitis? It seems to be a specific disease of the venous tree alone. The insignificance of an injury that may be the inciting cause of thrombophlebitis is illustrated in the following case, previously referred to

A nurse aged 23 struck the external surface of the calf of her leg against the crank handle of a Gatch bed. A small bruise appeared which she ignored for several days It persisted, however, and 10 days later presented evidence of local venous thrombosis, with redness, heat and cordlike swelling The patient was put to bed and cold packs were applied, but despite months of rest, the process continued locally At the time, anticoagulants were not available. The disease spread to involve most of the venous system of the body, including both arms and legs, the mesentery, abdominal wall, cerebral veins and probably the coronary veins The patient became a complete invalid as a result of what appeared to be a very minor but definite injury.

Innumerable cases could be cited of more severe injuries that have initiated prolonged invalidism from thrombophlebitis. One patient was carrying a box that slipped so that the edge fell against his right thigh. Another patient had a similar accident while he was carrying a large swordfish. A third received the full impact of a large netful of crude rubber which was being swung off a ship's side. Severe crushing of his abdomen led to multiple thromboses and serial thrombophlebitis.

The type of thrombophlebitis known as primary axillary venous thrombosis, which does not tend to spread, is discussed in Chapter XII.

CAPILLARY FRAGILITY

Capillary fragility may be increased by numerous poisons and chemicals in industry. The list of possible agents is long and not yet completed, and the subject is mentioned merely as a reminder that vascular manifestations of such poisoning should be kept in mind. In diagnosis it must be remembered that capillary fragility may be increased by infections, vitamin C deficiencies and other factors to which the patient is exposed away from his occupation.

LYMPHEDEMA

Lymphangitis and lymphedema may be a consideration in some instances If a company sends workers into an area where filariasis is endemic, the responsibility for development of the disease should be clarified A problem of this type recently arose. An international company wished to send an executive into a filariasis area for three years During the past war the employe had had filariasis with considerable edema of the left ankle, some of which remains. Despite his desire to take advantage of the opportunities which this assignment presented, we could only advise strongly against re-exposing himself to infestation and the risk of much more extensive disability.

It is impossible to discuss here all the hazards of industrial life with reference to their effects on workers in the infinite variety of environments encountered today. An effort has been made to present some of the problems encountered in our experience and to provide a suggestive guide to physicians who may be faced with similar situations in their own patients or in workers in industrial plants.

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CHAPTER XXX Amputation; Psychologic and Physical Care

UNFORTUNATELY, MANY patients with occlusive arterial disease still face the loss of one or more limbs For many the realization of this loss results in a severe psychologic shock, from which the patient may go into a depressive state. Recovery from this depression may be slow and difficult for the patient and the family

Although the technics of operative procedures are beyond the scope of this volume, there are certain frequently neglected aspects which fall within the province of the family physician.

PREPARATION OF THE PATIENT

The physician who has observed the patient for weeks or months and has watched a limb become progressively gangrenous is usually aware of the probability of amputation well in advance of the time for final decision Our experience has led us to believe that it is unwise to discuss the matter with the patient until the final decision has been arrived at from the medical point of view *Obvious indecision* on the part of the physician during several weeks may place the patient in a serious psychologic state, resulting in anorexia, malnutrition, depression and, if diabetes is present, disturbance of the diabetic control Such a situation may jeopardize the success of the amputation or even the patient's life.

When the decision seems clear from the medical point of view the family and the patient should be told The first question the patient usually asks is "how high?" It is difficult for laymen to understand that although only one or more toes may be gangre-

nous the only wise procedure is amputation below or even above the knee. This requires careful explanation that it is unwise to amputate below the level of a blood supply which will permit healing and that such a procedure might lead to multiple amputations, which are very undesirable. We have found that the following statement is generally most acceptable. "The surgeon will save as much tissue as he can He will try for a low amputation, but if the blood supply is too poor he will have to go high enough to insure healing. Preliminary studies, including oscillometric readings and arteriography, as well as clinical observations, are not as satisfactory as actual observation of bleeding vessels at the time of surgery for the final decision." Most patients are satisfied with this explanation.

The second question is usually "Will I ever walk again?" or, stated negatively, "Now I'll never walk again " It is the physician's responsibility to overcome this negative reaction We have found it helpful to recount the facts about the thousands of amputees from World War II who have learned to walk with a modern prosthesis and the many who are accomplished in certain types of athletic competition. Many patients who require amputation because of occlusive arterial disease are in the older age group, and we tell them about patients over 75 years of age who have learned to get about and enjoy life despite their prosthesis This is very important. If the patient does not get over this first psychologic hurdle, he or she may be a needless invalid for many years. Women are apt to be more sensitive than men regarding this problem, but they too can be brought to accept the situation philosophically The responsibility of the physician does not end with amputation It includes restoration of the patient to normal or near normal activity.

Preparation of the Stump for a Prosthesis

The operation must be so performed as to leave a good stump with adequate, firm flesh covering the bone Patients frequently

complain of pain and tenderness, but time and proper conditioning will result in a tough and useful stump capable of bearing weight for many years without breaking open under strain or chafing. We have seen an 88 year old patient who had an amputation at age 13 and has worn a prosthesis for 75 years without trouble.

The period of inactivity before and after the operation usually leads to atrophy of the muscles of the stump. These must be strengthened to permit use and control of the artificial limb. As soon as the stump is healed sufficiently, all joints which will be involved in the use of the artificial limb must be exercised for periods of 10 or 15 minutes to a total of two or more hours a day The joints should be moved in all directions possible, and exercise against pressure is excellent. General muscular exercise and reduction of any excessive weight become more important than ever as the patient begins to move about, first on crutches or a walker, then on the artificial limb.

It is also vitally important to produce shrinkage of the stump from the very beginning This is accomplished by the application of elastic (Ace type) bandages, with reapplication several times a day to keep constant pressure on the stump. If the shrinkage is not complete by the time the prosthesis is applied, the limb will shrink afterward, necessitating repeated addition of extra padding within the stump socket This is seldom satisfactory and often a new upper section must be made at considerable additional expense

cessively tight above, producing a tourniquet effect

A word of warning about the risk of contraction should be included. The tendency of the thigh to contract anteriorly and the leg to contract posteriorly is a natural one If this is allowed to persist, the use of a prosthesis may never be possible. When exercises are begun, someone must help the patient to extend the

stump and to learn how to do this himself The patient must then continue to work at this in the lying, sitting and, especially, the standing positions. The good leg must also be strengthened, since it must be prepared to bear an extra burden. Deep knee bends while the patient supports himself on a walker or the backs of two chairs will help with this problem.

When the patient first tries to use an artificial limb he is very apt to become discouraged The following factors are common causes of this.

1 General weakness and weakness of the stump
2 Lack of balance
3 Lack of skill in use of the prosthesis.
4 The unaccustomed weight and feel of the appliance
5 The tenderness and phantom pain, which usually wears off in a few weeks or, at the most, months
6 Final realization that, aside from the pain, this is an irrevocable situation.

Here too the physician must supply the needed encouragement and moral support to tide the patient through this crisis Walking must be practiced until it is a smooth, well co-ordinated movement, with the patient well balanced throughout the entire action When this has been achieved, the patient will usually be well adjusted and the physician will have fulfilled his responsibilty

APPENDIX · Method for Determining Plasma Prothrombin

(Link and Shapiro Modification of Quick Method)

Reagents

0.1 M sodium oxalate

Anhydrous, reagent grade sodium oxalate, 13 4 Gm. per 1,000 ml. of distilled water

0 85 per cent sodium chloride

Reagent grade sodium chloride, 8 5 Gm per 1,000 ml of distilled water

0 025 M calcium chloride

Anhydrous, reagent grade calcium chloride, 2 77 Gm per 1,000 ml of distilled water

Thromboplastin-calcium chloride mixture

To 50 mg. of Maltine thromboplastin in a small centrifuge tube, add 2.5 ml of 0 85 per cent sodium chloride Stir until a uniform suspension is obtained. This suspension is kept (with constant stirring) at 54–55 C. in a water bath for 10 minutes Cool to 25–26 C Add to this suspension 2.5 ml of 0.025 M calcium chloride solu-

slightly turbid supernatant fluid and use this solution in the determination Ampules of thromboplastin should be stored in the ice box.

Apparatus

1 Water bath, constant temperature 37 5 C. (Machlett #A84-410 metal, or A H. Thomas #9925-A glass, constant temperature water bath)

2. 100 × 12 mm. test tubes
3. Copper test tube racks (Army Medical type to hold 100 × 12 mm. test tubes)
4. Stop watch
5. Folin-Wu micro blood sugar pipets (Normax, graduated to contain 0 1 and 0.2 ml)
6. Kahn viewer (if Machlett #A84-410 type water bath is used)

Procedure

Blood samples are taken by mixing 4.5 ml of blood quickly with 0.5 ml of 0 1 M sodium oxalate The oxalated blood is centrifuged at 1,700 rpm for 10 minutes. The clear plasma is transferred with a pipet to a test tube Clotting time should be determined at once, but if stored in a refrigerator will remain fairly stable for several hours.

If prothrombin times are to be determined on 12 5 per cent diluted plasma as well as whole plasma, make dilution in another 100 × 12 mm. tube by diluting 0 1 ml. of whole plasma with 0 7 ml. of 0 85 per cent saline. Mix by tapping the lower end of the tube with the index finger

The 0.2 ml portions of thromboplastin-calcium chloride suspension are transferred into 100 × 20 mm. test tubes with a 0 2 ml. micro blood sugar pipet These tubes are placed in a rack along with the test tubes containing whole plasma or its dilution As soon as the contents have reached the bath temperature (usually 60 seconds) the clotting time of the plasma is determined as follows

With a micro blood sugar pipet transfer 0 1 ml. whole or diluted plasma to a tube containing 0 2 ml. of thromboplastin-calcium chloride suspension The plasma is quickly blown into the thromboplastin mixture while at the same time the stop watch is started. The tube is tapped sharply to mix the solutions A small Nichrome wire stirrer is introduced and the solution stirred at such a rate that the stirrer sweeps across the test tube from one side to the other two times per second. The process of stirring may take place out of the water bath and viewed under the magnifying glass of a Kahn viewer. The end-point, which is the formation of a fibrin clot, is that point at which the fibrin clot is sufficiently stable to be drawn to one side by the stirrer, thus bringing to view a clear area. Record seconds required to form the clot The clot is usually turbid, since the calcium oxalate formed on calcifying the oxalated plasma is enmeshed in the clot.

Normal standards

Whole plasma, 13–17 seconds

12.5% dilution, 35–42 seconds

tained easily and quickly.

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NOTE.—Asterisk (*) indicates reference to illustrations

A

4. Secretion of supraphysiologic amounts of cortisol by an adrenocortical tumor simulates the administration of exogenous cortisol in inducing features of Cushing's syndrome and in suppressing corticotropin secretion; the nontumorous adrenocortical tissue ceases to secrete cortisol and becomes *hypoplastic and unresponsive to corticotropin*. Removal of the adrenocortical tumor permits gradual recovery of normal pituitary-adrenal function.

5. Secretion of excessive quantities of corticotropin by an inappropriately overactive pituitary gland induces adrenocortical hyperplasia and excessive secretion of cortisol. The latter leads to the clinical and metabolic features of Cushing's syndrome.

6. In virilizing congenital adrenal hyperplasia the adrenocortical mechanism for synthesizing cortisol is grossly inefficient, and a compensatory increase in corticotropin secretion follows. Under the influence of large amounts of corticotropin the adrenal cortices become hyperplastic and *secrete large quantities of the androgenic "by-products" of cortisol. Administration* of cortisol in physiologic doses precludes the compensatory hypersecretion of corticotropin, thus permitting involution of the adrenal glands and a decrease in secretion of androgenic by-products to normal.

Valuable information concerning pituitary-adrenal function can often be obtained simply by determining plasma cortisol or by determining the quantity of cortisol metabolites (17-hydroxycorticoids) in the urine. Much more can be learned, however, by studying the effects which certain manipulations of pituitary or adrenal function have upon plasma or urinary corticoids. The most valuable of these are (1) tests of adrenocortical reserve, i.e., capacity to secrete cortisol in response to a standardized infusion of *corticotropin*, (2) *tests of pituitary reserve, i.e., capacity to secrete cortico*tropin in response to a reduced cortisol secretion and (3) tests of pituitary-

hydroxycorticoid values are used as the index of adrenocortical activity, it is possible under many of the conditions described to gain useful information from measurements of plasma 17-hydroxycorticoids, urinary 17-ketosteroids, or urinary "17-ketogenic" steroids. The propriety of measuring 17-hydroxycorticoids can be understood from the fact that under most conditions this measurement reflects specifically the concentration of cortisol and related compounds in body fluids. A relatively simple and reliable method of determining urinary 17-hydroxycorticoids is Peterson's modification[1] of the method of Silber and Porter.[2]

The tests to be described are based on observations of quantitative changes during biochemical manipulation of the pituitary-adrenal system.

It is clear that the diagnostic precision of the tests can be no better than the reliability with which the treatment schedule is followed, the reliability with which complete and carefully timed specimens are collected, and the technical precision with which the chemical determinations are performed. Unless all of these conditions can be assurred the tests may frequently be misleading.

Tests of Adrenocortical Reserve[3, 4]

Principle The continuous day to day secretion of normal amounts of corticotropin maintains the adrenal glands in a condition such that they are capable of a many fold increase in secretory activity in response to an increase in corticotropin whether endogenous or exogenous This capacity to secrete additional cortisol in response to a standard corticotropin test we refer to as adrenocortical reserve This is diminished in Addison's disease, due to loss of adrenocortical tissue; in congenital adrenal hyperplasia, due to gross inefficiency of the cortisol-synthesizing enzyme systems and in patients who lack corticotropin (e g., patients with panhypopituitarism, patients treated with corticoids, and certain patients with Cushing's syndrome due to autonomous adrenocortical tumors).

Standard Procedure. Urine is collected in 24 hour periods (8 a m to 8 a m) each day and preserved with 5 cc of 5 per cent thymol in glacial acetic acid Completeness of collection should be confirmed by determination of creatinine content After 1 or more control days the standard corticotropin test is performed by giving 50 USP units of corticotropin as a constant intravenous infusion over exactly 8 hours (8 a m to 4 p m.). The vehicle may be either 5 per cent dextrose in water or physiologic saline (the latter is preferable if Addison's disease is suspected) The test may be repeated on several successive days if adrenal insufficiency secondary to a lack of ACTH is suspected

Results' Approximately 98 per cent of normal adults excrete from 3 to 12 mg of 17-hydroxycorticoids/day. Lower values are obtained in children In response to a single standard corticotropin test about 98 per cent of normal adults excrete from 15 to 45 mg. of 17-hydroxycorticoids/day. Repetitive treatment with corticotropin progressively enhances the responsiveness of the adrenal glands, so that if the standard corticotropin test is performed on successive days, there is a stepwise increase in 17-hydroxycorticoid excretion from day to day.

In patients with Addison's disease the excretion of 17-hydroxycorticoids under control conditions ranges from 0 to 5 mg./day; thus, there is some overlap between the Addisonian and the normal. There is no overlap of Addisonian and normal responses to the standard corticotropin test, however, since no increase in 17-hydroxycorticoid excretion is found when corticotropin is administered to the patient with Addison's disease (fig 1).

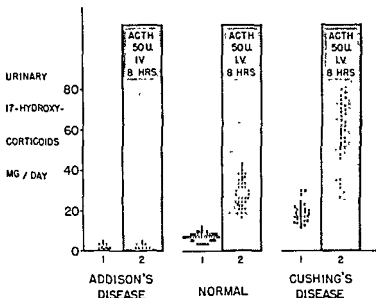


FIG 1—Urinary 17-hydroxycorticoid values (1) under control conditions and (2) in response to an eight hour intravenous infusion of ACTH in (A) patients with Addison's disease, (B) normal adults and (C) patients with Cushing's syndrome associated with adrenocortical hyperplasia

In other words, the patient with Addison's disease has no adrenocortical

to respond to further increases in corticotropin Such individuals may survive under ordinary circumstances but experience frank Addisonian crises under conditions such as trauma, infection or deprivation of food or salt.

Patients with frank panhypopituitarism, like those with Addison's disease, have subnormal 17-hydroxycorticoids Like the Addisonian, the patient with panhypopituitarism usually exhibits little or no response to a single standard corticotropin test Like the normal subject, however, the patient with panhypopituitarism responds to repetitive administration of corticotropin with a stepwise increase in 17-hydroxycorticoid excretion Adrenal responsiveness can be restored to normal by such treatment, but when exogenous corticotropin is withdrawn the adrenal glands quickly return to their unresponsive state

Patients who have received exogenous cortisol-like steroids often exhibit hypopituitarism with respect to corticotropin As in panhypopituitarism the response of *such patients to an initial standard corticotropin test may*

It is clear that the diagnostic precision of the tests can be no better than the reliability with which the treatment schedule is followed, the reliability with which complete and carefully timed specimens are collected, and the technical precision with which the chemical determinations are performed. Unless all of these conditions can be assurred the tests may frequently be misleading.

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large quantities, thus suppressing corticotropin secretion, and atrophy of the non-tumorous adrenocortical tissue follows. This situation is analogous to the one in which exogenous cortisol suppresses corticotropin and induces adrenocortical atrophy. By repetitive administration of corticotropin it is possible to correct the unresponsiveness of the non-tumorous adrenal tissue. Therefore, beginning from a high baseline (due to cortisol from the autonomous tumor) it is possible to bring about a further stepwise increase in urinary 17-hydroxycorticoids through a series of corticotropin tests.

Patients with Cushing's syndrome and bilateral adrenocortical hyperplasia usually have supernormal adrenal responsiveness to standard corticotropin tests (fig. 1), and this is probably a consequence of chronic mild excess of corticotropin. Following successful treatment of Cushing's syndrome by any means responsiveness is normal. Supernormal adrenocortical responsiveness is not invariably seen in Cushing's syndrome and adrenal hyperplasia; of our last 27 patients with this condition 4 have had normal adrenal responsiveness. Three of the four were less than 15 years of age.

Following adequate treatment by means of subtotal adrenalectomy patients with Cushing's syndrome due to adrenocortical hyperplasia have little or no adrenocortical reserve. Such patients resemble those with Addison's disease in that their adrenal remnants are already functioning maximally. This statement would not apply to patients in whom adrenal resection was not radical enough to bring about a substantial decrease in 17-hydroxycorticoids.

In patients with virilizing congenital adrenal hyperplasia adrenocortical reserve is moderately or markedly diminished. In this condition, the adrenocortical mechanism for synthesizing cortisol is grossly inefficient, and consequently there is a compensatory increase in secretion of corticotropin. The inefficient adrenal cortex is often able then to secrete normal quantities of cortisol, but in the process there is gross hypersecretion of the by-products and precursors of cortisol, some of which are androgenic and some of which are excreted as 17-ketosteroids. In the more severe cases, even maximal stimulation of the adrenal cortex fails to raise cortisol secretion to normal; these individuals exhibit no adrenocortical reserve when the standard corticotropin test is administered. In less severe cases submaximal adrenocortical stimulation is sufficient to bring cortisol secretion up to normal. In response to the maximal stimulation of the standard corticotropin test, the adrenal glands of these patients can secrete additional cortisol, but the increments in cortisol secretion are less than those seen in normal individuals.

TESTS OF PITUITARY RESERVE[5, 6]

Principle. Normally a decrease in cortisol secretion results in an increase in secretion of corticotropin by the pituitary. The capacity of the pituitary

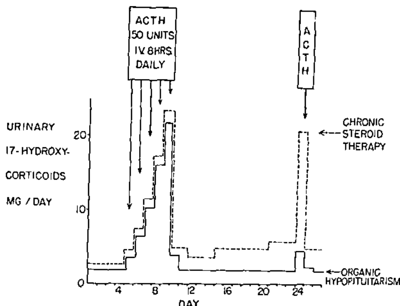


Fig 2—Urinary 17 hydroxycorticoid values under control conditions and in response to eight hour intravenous infusions of ACTH in (A) a patient with frank panhypopituitarism (a sequel of postpartum hemorrhage), and (B) a patient with rheumatoid arthritis who had just been withdrawn from corticoid therapy after one year of continuous treatment

be negligible, but with repetitive stimulation adrenal responsiveness can be restored to normal An important difference between the patient with organic panhypopituitarism and the one whose secretion of corticotropin has merely been suppressed by exogenous corticoids is seen in the sequence of events following complete withdrawal of exogenous corticosteroids and corticotropin Over a period varying from several days to several weeks when corticotropin has merely been suppressed there will be a gradual recovery of adrenocortical reserve whereas with organic panhypopituitarism there will not (fig 2)

Incidentally, since exogenous corticotropin acts directly on the adrenal cortex, it is possible to rule out the diagnosis of Addison's disease without withdrawing supportive corticosteroid therapy *For* example, a patient suspected of Addison's disease could be treated with desoxycorticosterone acetate 5 mg /day and dexamethasone 0 5 mg every eight hours throughout the study; unless the patient on such a regimen has Addison's disease corticotropin tests on five successive days should always induce a substantial rise in urinary 17-hydroxycorticoids.

Certain patients with Cushing's syndrome due to adrenocortical tumors have little or no adrenocortical reserve. In this group of patients the tumors are unresponsive to corticotropin The autonomous tumors secrete cortisol in

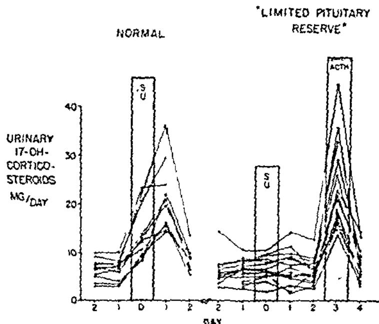


FIG 3—Urinary 17 hydroxycorticoid values under control conditions and in response to SU 4885 in (*left*) normal adults and (*right*) 16 patients with "limited pituitary reserve." The fact that all 16 patients were able to respond to standard ACTH tests (extreme right) indicates that their failure to respond to SU 4885 was not owing to lack of adrenocortical reserve

corticoids and none of them required adrenal substitution therapy under ordinary conditions. They did not, therefore, fall into the category of frank panhypopituitarism All 16 of them responded to a standard corticotropin test, so they did not fall into the category of limited adrenocortical reserve Since they did not respond to an SU 4885, it is inferred that the corticotropin-secreting mechanism lacked the capacity to increase its activity in the face of requirements for additional corticotropin In short, pituitary "reserve" was limited. Incidentally, 5 of the 16 patients were known to have suffered adrenal insufficiency during episodes of infection or trauma, suggesting once again that although their corticotropin-secreting mechanisms were adequate to meet everyday requirements they were not capable of increased activity in response to further needs for corticotropin

Not all patients with pituitary lesions have limited pituitary reserve. In the study referred to above pituitary reserve was found to be grossly normal in 3 of 6 patients with chromophobe adenomas, 3 of 5 patients with acromegaly and 3 of 6 patients with cachexia. Lack of reserve capacity to secrete corticotropin was not necessarily correlated with thyroid function

gland to secrete corticotropin in amounts greater than required under ordinary conditions might be referred to as pituitary reserve. If the test subject has adrenocortical reserve it is possible to evaluate major changes in endogenous corticotropin by observing changes in adrenal steroid secretion. A convenient way of stimulating corticotropin secretion is to inhibit cortisol synthesis by means of a selective inhibitor of 11β-hydroxylation Under such conditions an increase in corticotropin secretion results in a rise in adrenocortical secretion of 11-desoxy-cortisol or compound S. Compound S and its metabolite tetrahydro-S are measurable as 17-hydroxycorticoids in blood and urine. Since compound S is ineffectual as a suppressor of corticotropin, the greater the inhibition of cortisol secretion the greater will be the increase in corticotropin secretion and consequently the greater will be the rise in adrenocortical secretion of compound S. Therefore, in subjects with normal adrenocortical reserve and intact pituitary function, the administration of an 11-β-hydroxylase inhibitor results in large increases in *total* 17-hydroxycorticoids, due to increases in compound S and its metabolites.

Standard Procedure Urine is collected for 17-hydroxycorticoid assay on several successive days as outlined in the procedure for testing adrenocortical reserve After 2 control days the 11-β hydroxylase inhibitor 2 methyl-1,2-bis-(3-pyridyl)-1-propanone (SU 4885—Ciba) is administered orally in doses of 500 mg every 4 hours for 6 doses (first dose 8 a m., last dose 4 a m) Since rapid absorption of SU 4885 may lead to vertigo, it is advisable to administer each dose following a small meal or a glass of milk After two more control days, a standard corticotropin test may be performed in order to evaluate adrenocortical reserve (the test of pituitary reserve is meaningless in patients who cannot respond to corticotropin)

Results: "Normal" individuals (those in whom there is no reason to suspect pituitary or adrenal dysfunction) respond with two to fourfold increases in urinary 17-hydroxycorticoids. The increase is appreciable during the 24 hour period during which SU 4885 is administered, but it is usually *greater during the following 24 hour period*

Of course patients with negligible adrenocortical reserve fail to respond to SU 4885 with an increase in 17-hydroxycorticoids.

The term *limited pituitary reserve* has been applied to a group of patients who are apparently unable to respond to SU 4885 with an increase in 17-hydroxycorticoids even though the control 17-hydroxycorticoids are normal and even though they are capable of responding to exogenous corticotropin (fig. 3) In one[6] series of 16 such patients it was noted that 8 had pituitary tumors (6 chromophobe and 2 eosinophilic), 4 had previously been successfully treated for Cushing's disease by means of pituitary irradiation, 1 had post-traumatic diabetes insipidus, and 3 were cachectic from various causes. All 16 of these patients had normal 17-hydroxy-

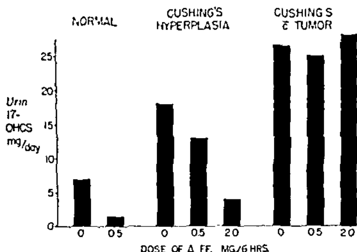


FIG 4—Urinary 17-hydroxycorticoids under control conditions and during the second day of treatment with various dosages of ΔFF in normal adults (average of 50 subjects), patients with Cushing's syndrome associated with adrenocortical hyperplasia (average of 23 patients) and patients with Cushing's syndrome associated with adrenocortical tumors (average of 8 patients)

corticoids in excess of 12 mg /day and fail to exhibit a decrease to less than 4 mg /day in response to ΔFF In many cases, the 17-hydroxycorticoids are as high during ΔFF treatment as they were during control periods

In response to the larger dose of ΔFF, 2.0 mg every six hours, patients with Cushing's syndrome due to adrenal hyperplasia exhibit reduction in 17-hydroxycorticoids, almost always to less than 50 per cent of the control values. This may mean that the adrenocortical hypersecretion is dependent on corticotropin 17-Hydroxycorticoid levels of patients with Cushing's syndrome due to autonomous adrenocortical tumors are not suppressible even with these large doses of ΔFF. This may mean that the high concentrations of cortisol from the tumor have already suppressed corticotropin.

Patients who have been successfully treated for adrenal hyperplasia by irradiation of the pituitary or by subtotal adrenalectomy exhibit normal 17-hydroxycorticoids but show abnormal resistance to the suppressive influence of ΔFF. This may mean that the treatment did not correct the fundamental disorder in this disease Rather, pituitary irradiation is effective because it compromises pituitary reserve, and subtotal adrenalectomy because it compromises adrenocortical reserve.

Patients who have been successfully treated for Cushing's syndrome by surgical removal of adrenocortical tumors subsequently exhibit perfectly normal suppressibility of the pituitary-adrenal system. Continued nonsuppressibility following tumor resection might indicate either of two condi-

or with urinary gonadotropin From the available evidence it appears that the SU 4885 test is a sensitive one; it has not been established that failure of the corticotropin-secreting mechanism to respond to SU 4885 implies that it would invariably fail to respond to intense stimuli such as those encountered in major surgical procedures.

Individuals who are receiving exogenous cortisol-like steroids or exogenous corticotropin in large doses do not of course respond to SU 4885 with increased 17-hydroxycorticoid secretion, and it is important that the patient should not be receiving such agents during or for two days preceding the SU 4885 test

Patients with virilizing congenital adrenal hyperplasia and those with primary hypothyroidism have been found to respond to SU 4885 provided they respond to corticotropin.

Corticotropin Suppression Tests

Principle Normally the secretion of corticotropin by the pituitary is subject to regulation by the concentration of cortisol in body fluids. In the performance of corticotropin suppression tests it is convenient to employ steroids which will themselves not be measured as plasma or urinary 17-hydroxycorticoids A synthetic steroid which until recently has been unique in its value as an corticotropin suppressing agent is Δ^1-9α-fluoro-hydrocortisone ("ΔFF"). The peculiar merit of ΔFF is that it is about 30 times as potent as cortisol with respect to corticotropin suppression and related biologic activities It can be used in doses which are so small that they make no contribution to the corticosteroids as measured chemically.[7] The recently developed 16α-methyl analog of ΔFF, dexamethasone, may be used in corticotropin tests, but other corticosteroids cannot unless their corticotropin-suppressing potencies are known precisely and dosages are adjusted accordingly.

The standard corticotropin suppression test is of value in the diagnostic evaluation of patients suspected of having Cushing's syndrome.

Standard Procedure Urine is collected for 17-hydroxycorticoid assay on several successive days After two control days either ΔFF or dexamethasone is administered orally in doses of 0 5 mg every 6 hours for at least 8 doses If suppression of 17-hydroxycorticoids does not occur with this dose of ΔFF, further information can be gained by repeating the procedure using doses of 2 0 mg every six hours for at least 8 doses.

Results Normal individuals (those in whom there is no reason to suspect pituitary or adrenal dysfunction) respond with a decrease in urinary 17-hydroxycorticoids to less than 2 mg./day by the second day of treatment, and the values remain low for as long as ΔFF is continued.

Patients with Cushing's syndrome (fig. 4) almost always have 17-hydroxy-

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[7] ——: Δ^1,9α-fluorohydrocortisone a new investigative tool in adrenal physiology. J Clin. Endocrinol *16* 557, 1956

tions· (1) The tumor might have extended beyond the portion resected or (2) the "tumor" might have been incidental to a fundamental process of adrenocortical hyperplasia. These two conditions should be distinguishable from each other by the response to repeated tests with the larger dosages of ΔFF.

Exceptional Responses to ΔFF. Occasionally, patients with acromegaly exhibit resistance to the suppressive action of ΔFF similar to that observed in patients with Cushing's syndrome and adrenal hyperplasia.

Among patients with Cushing's syndrome due to adrenal hyperplasia the degree of resistance to the suppressive influence of ΔFF varies considerably from one individual to another. Apparently, there is a spectrum of degrees of suppressibility among patients with Cushing's syndrome with adrenal hyperplasia In time, cases may be encountered in which the pituitary-adrenal system is almost normally suppressible with the smaller dose of ΔFF, and other cases may be encountered in which the pituitary-adrenal system may be almost completely resistive to suppression by the larger dosages of ΔFF The author would urge a conservative policy in either situation: that great caution be exercised in rendering a final diagnosis of Cushing's syndrome in the readily suppressible case and that adrenal exploration be performed in the completely nonsuppressible case.

Occasionally, patients with equivocal clinical pictures of Cushing's syndrome and slightly increased 17-hydroxycorticoids have exhibited slight

Cushing's syndrome or are merely normal variants.

Conclusions

Many endocrinopathies can be viewed as disorders of homeostasis in which the secretory mechanism in question is either inadequately responsive to stimuli or is resistive to those influences which normally suppress hormone secretion With the standard corticotropin test it is possible to find inadequacies of adrenocortical responsiveness With the standard SU 4885 test it is possible to show inadequacies of the corticotropin-secreting mechanism. With the standard ΔFF test it is possible to show that in patients with Cushing's syndrome the corticotropin-cortisol secretory system is abnormally resistive to suppression

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venience and can therefore be applied to clinical problems which require the assay of large numbers of urine samples. Considerable efforts have been directed towards establishing the reliability of some of these methods under a variety of conditions (see, for example, refs. 10–12), and in turn the "established" methods have acted as controls for the newer methods as they have been developed. As a result, the range of applicability of these methods can be defined, and provided this range is observed, confidence can be placed in the results obtained. This chapter deals with the application of these newer assay technics to clinical problems. No attempt will be made to describe them individually or to discuss the methods employed for establishing their reliability. The term "total estrogens" will imply the sum of estrone, estradiol-17β and estriol.

Clinical Application of Estrogen Assays

Results in Women of Child-Bearing Age

The Ovulatory Menstrual Cycle. A characteristic pattern of estrogen excretion is found during the menstrual cycle. This is now so well established that it provides a useful preliminary check on the reliability of a new assay technic. The characteristic features of this pattern are illustrated in figure 1, which shows the maximum, mean and minimum values for the daily excretion of estrone, estradiol and estriol by 16 women throughout their menstrual cycles. The amounts of the three estrogens excreted generally rise and fall together. Quantitatively, estradiol-17β is the minor urinary estrogen, estrone and estriol may be excreted in equivalent amounts or estriol may be the major estrogen. The amounts excreted are low during the first week of a 28 day cycle, and then rise to a well defined peak, termed the "ovulatory peak," or "follicular maximum," which occurs on or about the fourteenth day of the cycle. This is followed by a short period of decrease and then by another rise, termed the "luteal maximum." This second peak is usually lower than the follicular maximum and occasionally it may be absent. During the last few days of the cycle the estrogen excretion falls and then menstruation occurs.

The shape of the ovulatory peak is highly characteristic: it is shown by all three estrogen fractions, the rise to the peak is usually gradual, and the subsequent fall is often abrupt, the rise and fall in estriol tends to lag slightly behind the rise and fall in estrone and estradiol; and the interval of time between the peak and the onset of menstruation is usually about 14 days.

It is reasonable to believe that this pattern of urinary estrogen excretion reflects the following possible sequence of events occurring in the ovary. The secretion of the primary ovarian hormones, estrone and estradiol,

10

Clinical Significance of Urinary Estrogen Determinations

By J. B. BROWN, M Sc., PH D.

INTRODUCTION

AT THE TIME OF WRITING, 10 metabolites of the primary estrogenic hormones, estrone and estradiol-17β have been isolated from human urine and identified. These are present as water-soluble conjugates the most important of which are the glucuronides They include estrone and estradiol-17β themselves and a number of their hydroxy, oxo and methoxy derivatives [1, 2] It is also certain that two and probably more similar compounds have yet to be discovered

Experiments in which isotopically labeled estradiol-17β has been administered to human subjects indicate that this hormone is very rapidly metabolized and excreted within a period of approximately 12 hours, partly in the urine and partly in the bile. The biliary metabolites appear to be the same as those excreted in the urine [3] They are mainly reabsorbed from the gut and re-excreted in the urine and bile. Eventually, during a period of two to three days, the major portion of the administered hormone is excreted in the urine and a small amount is excreted in the feces.[4, 5] After hydrolysis of the conjugates, the urinary component is found largely in the neutral plus phenolic fraction and can be accounted for mainly as the known estrogens. There appears to be no degradation of the steroid nucleus during this process

At present, there are reliable methods for measuring only 3 of the estrogens in urine, namely estrone, estradiol-17β and estriol Obviously, a method for measuring all the urinary metabolites of estrone and estradiol would be highly desirable. It would provide an accurate measure of the amounts of the primary hormones produced in the body, it would yield information concerning the various metabolic processes and their relative importance in health and disease and it might also indicate whether some of the metabolites themselves, apart from being excretory products, have important functions in the body Nevertheless, useful results are being obtained through the application of methods which measure estrone, estradiol-17β and estriol only. Until recently, these restricted methods were generally based on bioassays which suffered from a number of disadvantages and were extremely laborious. During the last four years, a number of chemical methods has been described for the assay of one or all of these 3 estrogens (see, for example, refs. 6–9). These chemical methods have the advantage of con-

corresponding changes in the ovary A number of attempts has been made to prove this point. In a study involving over 100 women, Brown, Kellar and Matthew[13] invariably observed a characteristic "ovulatory" peak whenever ovulation occurred as judged by the usual criteria of endometrial biopsy, basal temperature records and urinary pregnanediol excretion However, since all these criteria depend on the formation of a functioning corpus luteum, these workers could not establish that an "ovulatory" peak without accompanying luteal changes, would in itself be proof of ovulation. In this series, the period of time between the onset of the previous phase of bleeding and the "ovulatory" peak varied in different subjects from 5 to 92 days and between the peak and the onset of the next bleeding phase from 11 to 16 days Brown, Klopper and Loraine[14] found that the midcycle estrone-estradiol peak occurred one to four days before both the rise in basal temperature and the luteal phase increase in urinary pregnanediol output, and either coincided with the midcycle peak of urinary gonadotropin excretion or preceded it by an interval of up to four days. They also reported a case in which an insemination performed on the day of the estrone-estradiol peak resulted in a successful pregnancy whereas several inseminations timed on the basis of the change in basal temperature had been unsuccessful

It can be concluded that measurements of the daily output of estrone, estradiol-17β and estriol in the urine throughout the menstrual cycle, provide a reliable picture of ovarian activity And, in fact, the finding of a characteristic "ovulatory" peak of excretion does seem good evidence that ovulation has occurred and probably also indicates when it occurred This method of testing for ovulation does not depend on the presence of a functioning corpus luteum as do other methods, which can be an advantage, for example, when testing the effect of progestational compounds on ovarian function

Amenorrhoea Brown et al[15] studied 23 patients suffering from amenorrhoea These were divided into four groups as follows:

Group I comprised 3 cases of primary amenorrhoea due to congenital absence of uterus and vagina. Cyclical changes in urinary estrogen output were observed in all cases In 2, the characteristic "ovulatory" peak followed by a luteal maximum was demonstrated, and in both of these the occurrence of ovulation was confirmed by pregnanediol assays These cases therefore show that normal ovarian function is possible in the absence of the target organ, the uterus

Group II comprised 8 cases, age 20 to 38, one with primary amenorrhoea, the others with secondary amenorrhoea These patients did not subsequently menstruate and were therefore classified as menopause praecox. In all cases, the endometrium was atrophic and the estrogen output was low.

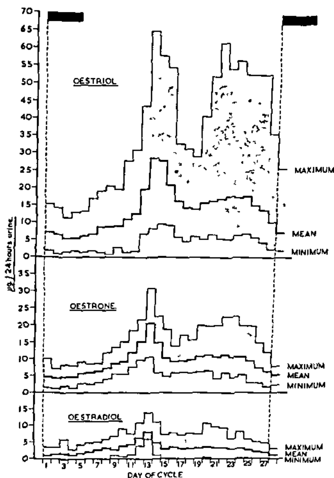


FIG 1—Mean, maximum and minimum quantities of urinary estriol, estrone and estradiol-17β from 16 women, aged 18 to 41 years, with normal menstrual cycles Time between onset of bleeding (day 1) and ovulatory peak of estrone/estradiol varied from 10 to 18 days, (mean 13 days), and between estrone/estradiol ovulatory peak and first day of next menstruation, from 12 to 16 days (mean 14 days) Curves were constructed by superimposing individual curves in such a way that each of the estrone/estradiol ovulatory peaks coincided with day 13 of the composite curves Solid black bar = menstruation.

increases as the size of the follicle increases and reaches a peak just before rupture at ovulation The derangement of the follicle following rupture results in a fall in estrogen secretion. Growth and regression of the corpus luteum cause a second rise and fall in estrogen secretion Since estrone and estradiol are metabolized and eliminated very rapidly in the urine as their conjugates and slightly less rapidly as estriol, it follows that the fluctuations in urinary estrone and estradiol should be closely related in time to the

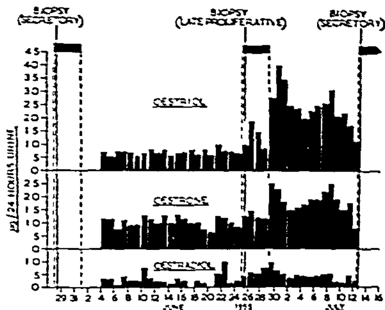


Fig. 2—An anovulatory menstrual cycle followed by an ovulatory menstrual cycle [12]
Solid black bar = menstruation

estrogen assays in 14 patients who were being studied for cystic glandular hyperplasia. They found that they could divide the patients into two groups according to the estrogen output.

1. Patients in whom the urinary estrogen output remained more or less constant at 30 to 40 micrograms total estrogen/24 hours between episodes of bleeding, this is analogous to the pattern found during anovulatory menstrual cycles except that the output is maintained at a higher rate. Such a case is illustrated in figure 3.

2. Patients who showed a single rise and fall in estrogen output between bleeding phases, this differed from an ovulatory peak in that higher values were reached and these were maintained for a longer period of time. Such a case is illustrated in figure 4. Here the total estrogen output remained above 35 micrograms/day for 20 days and reached 80 micrograms, a value rarely reached during the normal menstrual cycle. It was observed that ovulation sometimes occurs between phases of this type.

These workers concluded that cystic glandular hyperplasia of the endometrium is found in association with total urinary estrogens which have been maintained for some time in the region of 30 micrograms/day or more, and that bleeding from this type of endometrium may occur while the output is constant, while it is rising or while it is falling. After a period of

The ranges of values in micrograms/24 hours were as follows: estrone 1 0 to 4 7 (mean 3.2), estradiol nil to 3.1 (mean 0.7), estriol nil to 5.0 (mean 2.4), total 1.8 to 10.0 (mean 6.3).

Group III consisted of 11 patients, who, after periods of amenorrhoea lasting from three years to two months, subsequently menstruated These were, therefore, examples of temporary suppression of ovarian function The results of estrogen assays ranged from the low levels found in group II to those found during the normal menstrual cycle.

Group IV comprised two patients with functioning ovarian tumors Both were excreting approximately 13 micrograms total estrogens/day It was suggested that these amounts were derived from the tumor and were sufficient to suppress normal ovarian function

The Anovulatory Menstrual Cycle. Five cases exhibiting anovulatory menstrual cycles were described by Brown et al [13] These all had histories of irregular episodes of bleeding, although the bleeding phases under study occurred at approximately regular monthly intervals Diagnosis in all cases was based on endometrial biopsies. In a study of estrogen excretion in 27 women having apparently normal menstrual cycles, the writer (unpublished observations) has encountered anovulatory cycles in 3 These were diagnosed on the basis of basal temperature records and pregnanediol assays The results obtained in these anovulatory cycles were similar in all respects to those reported by Brown et al.[13]

Figure 2 illustrates the estrogen values found during these anovulatory menstrual cycles. In the case shown, an anovulatory cycle was followed by an ovulatory one. The characteristic features of the anovulatory menstrual cycle are. (1) The estrogen output remains more or less constant between episodes of bleeding and shows only minor day to day fluctuations This contrasts with the rhythmic changes which occur during the ovulatory cycle (2) The estrogen output is maintained at higher levels than those found in women with an atrophic endometrium and experiencing complete amenorrhoea The daily excretion values found in 116 determinations performed during 11 anovulatory cycles in 6 women ranged as follows estrone 3 to 13 micrograms (mean 6.4), estradiol nil to 10 2 (mean 2 4), estriol 5 to 21 μg (mean 9.4) total 9–33 (mean 18.2) It seems that these amounts of urinary estrogens reflect threshold production of estrogens by the ovaries which is sufficient to stimulate growth of the endometrium As the endometrium builds up under this steady stimulation, it apparently becomes unstable and breaks down from time to time resulting in anovulatory bleeding from a proliferative endometrium. Unlike normal menstruation this bleeding occurs without withdrawal of the estrogenic (and progestogenic) stimulation.

Cystic Glandular Hyperplasia: Brown et al.[13] recorded the results of

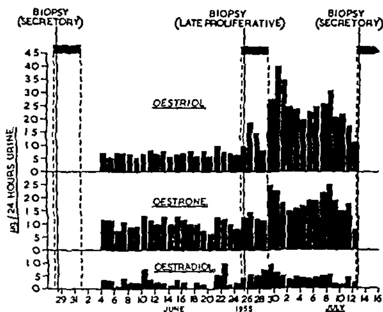


FIG. 2—An anovulatory menstrual cycle followed by an ovulatory menstrual cycle [13]
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estrogen assays in 14 patients who were being studied for cystic glandular hyperplasia. They found that they could divide the patients into two groups according to the estrogen output

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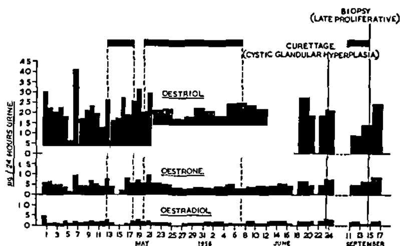


Fig 3—Cystic glandular hyperplasia (constant estrogen excretion)[13] Solid black bar = menstruation

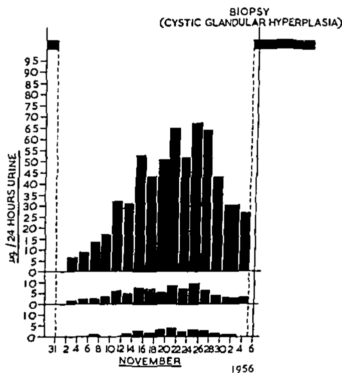


Fig 4—Cystic glandular hyperplasia (fluctuating estrogen excretion)[13] Solid black bar = menstruation

elevation, the estrogen output may fall to very low values. As this often coincides with the onset of bleeding, it is common to find patients who are bleeding from a well developed cystic glandular hyperplasia and who are at the same time excreting very small amounts of estrogens.

Results in Postmenopausal Women

Normal Values: A number of centers have recently reported values for the output of urinary estrogens by postmenopausal women. The most carefully controlled series is that reported by McBride.[14] This worker assayed 24 hour urine specimens collected twice weekly over a period of six to eight weeks from 7 women who were 2 to 26 years past the menopause. All 7 subjects had an atrophic endometrium and none had experienced postmenopausal bleeding. There was no evidence of any cyclic changes in estrogen output in any individual although the amounts excreted could vary considerably from day to day The mean excretion values for each of the 7 individuals are summarized in table 1. There was no correlation between estrogen output and time past the menopause.

Postmenopausal Bleeding: Brown et al.[13] investigated 23 women with postmenopausal bleeding Assays were usually performed on at least two 48 hour collections of urine. These cases were divided into 3 groups

1. Ten patients with an inactive endometrium, the bleeding in 5 of these was due to an adenocarcinoma of the body of the uterus, in 1 to cervical ulceration, in 1 to a cervical polyp, and in 1 to localized endometrial polyps. The cause of bleeding was not ascertained in 2

2. Six patients in whom the endometrium was not examined; 5 of these

TABLE 1—*Estrogen Output in Postmenopausal Women (Results in μg/24 hr urine)*

	Normal*	Postmenopausal Bleeding†		
Endometrium *No of Cases*	*atrophic* *7*	*atrophic* *10*	(cervical carcinoma) 6	*active* *7*
estrone range	1.1–2.7	0.3–2.4	0.9–3.1	1.4–15.4
mean	1.9	1.3	1.6	4.6
estradiol range	0.2–1.1	0–1.4	0–1.7	0–2.0
mean	0.6	0.3	0.4	0.7
estriol range	1.6–5.4	2.2–7.5	2.0–6.6	1.2–21.1
mean	3.3	3.9	3.6	10.9
total range	3.1–8.1	3.2–9.0	3.6–8.9	2.6–44.0
mean	5.8	5.5	5.6	16.2

* From McBride[14]

† From Brown et al[13]

had a squamous epithelioma of the cervix and 1 had a cervical adenocarcinoma.

3 Seven patients who showed endometrial changes consistent with estrogenic stimulation, 3 of these had ovarian tumors which were probably the source of the estrogen.

The mean excretion values for each individual in these groups are summarized in table 1.

The estrogen values found in groups 1 and 2 were the same as those found in the normal group The apparent anomaly of the low values found in some of the patients with an active endometrium was discussed in the section dealing with cystic glandular hyperplasia.

Cancer of the Breast. There has been much speculation on the possible relationship between estrogen secretion and mammary carcinoma. This has been stimulated in recent years by the finding that hypophysectomy or bilateral oophorectomy and adrenalectomy may be beneficial to a proportion of patients with this disease Consequently, attempts have been made in a number of centers to clarify these findings by laboratory analyses. Great difficulties have been encountered because the assay methods available are no longer reliable at the very low rates of estrogen excretion found in these patients.

Brown[17] was unable to find any convincing differences in the output of endogenous estrogens in a group of 27 postmenopausal women with recurrent breast cancer and a comparable control group. Estradiol-17β was administered to subjects in both groups to determine whether any differences could be detected in their metabolism of estrogens The percentage of the dose recovered in the urine as the 3 estrogens was the same in the two groups However, in the cancer group, estriol usually accounted for a higher proportion of the "total" urinary estrogens than in the control group This was also reflected in the output of endogenous estrogens. Such a change in the relative importance of estriol has been observed in other conditions

A number of workers[15, 18-22] measured the urinary output of estrogens before and after oophorectomy, adrenalectomy and hypophysectomy In postmenopausal women no change in estrogen output could be detected following oophorectomy Adrenalectomy and hypophysectomy usually reduced the output of urinary estrogens, but the results of the assays were usually so unreliable at the quantities being measured that it was impossible to determine whether the estrogen output had been abolished or not. However, results obtained by biological methods indicated that some patients continue to excrete estrogens in the urine after these operations.[23, 21] No convincing correlation between the output of estrogens in the urine and the clinical response to various forms of treatment could be found by any

of the workers. Obviously more sensitive methods of assay are required for this type of investigation.

A number of the above workers administered corticotropin (ACTH) to some of their patients This elicited a great increase in urinary estrogens when the adrenals were intact but failed to do so after bilateral adrenalectomy. These results provided good evidence, which had hitherto been lacking, that the adrenals are important sources of urinary estrogens in the human being They further showed that adrenalectomy was effective in removing all the tissue which responds to corticotropin. The rise in estrogen output which follows the administration of corticotropin may equal that which occurs at ovulation during the menstrual cycle. From a consideration of the relative amounts of the three estrogens excreted at this time, Brown, Falconer and Strong[13] concluded that the adrenal cortex secretes the same estrogens as the ovaries, namely estradiol-17β and estrone, and, when suitably stimulated, has as great a capacity for doing so as the ovaries at the height of their activity during the menstrual cycle.

Normal Men and Men with Coronary Disease

The higher incidence of myocardial infarction in men of all ages and in women after the menopause as compared with that found in women of child-bearing age, suggests that estrogens, or lack of them, might play an important role in the onset of this disease. This suggestion is further supported by the observation that male South African Bantus, who frequently show signs of estrogenic changes such as gynecomastia, are relatively immune to coronary disease Consequently, a number of South African workers have compared the estrogen excretion of healthy European men, European men with acute myocardial infarction and Bantu men The results are summarized in table 2

Statistical analysis of the results showed differences (P = <0.005) between the following groups (1) In the healthy Europeans, the output of all 3 estrogens was higher in the older age group This was especially so in the estriol fraction (2) Compared with healthy Europeans of similar age, the men with myocardial infarction excreted less estradiol, estrone and total estrogens, but the same amount of estriol The proportion of estriol to total estrogens was therefore higher in the group with myocardial infarction (3) The total estrogen output was higher in the Bantu than in the healthy European of comparable age, the increase being confined entirely to the estradiol fraction This difference between Bantu and European men was also observed by Bloomberg, Miller, Keeley and Higginson.[24] These workers concluded that the Bantu is less efficient in metabolizing estradiol than the European

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th cirrhosis of the liver and a control group of 10 healthy men. Individual lues were not reported, but as a group, the patients with cirrhosis ex-eted larger amounts of total estrogens than the control group, and again, is increase was confined mainly to the estriol fraction. The writer (un-iblished observations) has also found that the output of urinary estrogens ay sometimes be increased in liver disease, and that this increase usually cludes the estriol fraction. These findings are not in accord with the belief iat estrogen metabolism is impaired in these cases. In fact, the moderately iseased liver seems to be even more effective in metabolizing estrogens ian the normal, at least in so far as the pathway to estriol is concerned.

Adrenocortical Tumors and Adrenocortical Hyperplasia

A raised estrogen output is a common finding in patients with adreno-ortical tumor and adrenocortical hyperplasia. For example, Eberlein et al.[9] ound estriol excretion to be 3 to 60 times the normal in 10 children and 2 young women with adrenal hyperplasia. The children excreted amounts which ranged from 6 micrograms/24 hours by a girl 3 months old to 113 micrograms/24 hours by a girl 2 years old, the women excreted from 61 to 125 micrograms estriol/24 hours. In all cases the estrogen excretion was greatly reduced by treatment with cortisone or its analogues. Brown, Bulbrook and Greenwood[18] estimated the amounts of estrone, estradiol and estriol excreted in the urine by 4 patients with adrenal carcinoma. One was excreting quantities which were within the normal range for her age and sex, the others were excreting 10 to 20 times the normal amounts. The writer has observed daily excretion values as high as 614 micrograms estrone, 64 micrograms estradiol and 640 micrograms estriol in a patient with an adrenal tumor, these were reduced to normal values by removal of the tumor.

Provided allowance is made for a possible ovarian contribution, the output of urinary estrogens appears to be a sensitive and reliable index of abnormal adrenal function.

The Relationship Between Urinary Estrogen Excretion and Clinical Signs of Estrogenic Activity

The Histologic Appearance of the Endometrium

From their study of 75 patients with a variety of gynecologic disorders, and 16 women having normal menstrual cycles, Brown et al.[12] were able to show a close correlation between the amounts of the 3 estrogens excreted in the urine and the state of the endometrium. They divided their subjects into two main groups according to whether they [illegible] eting amounts of estrogens which remained more or less cons

TABLE 2—*Urinary Estrogen Excretion by Healthy European Men, European Men with Acute Myocardial Infarction and Bantu Men*

	Age (yrs)	Estrone	Estradiol	Estriol	Total
Healthy Europeans					
(21) Range	20–48	1 7–9 8	0–3 1	0.6–9.9	3 8–15 4
(21) Mean	31	4 3	1 1	2 6	8 0
(20) Range	45–65	2 8–12 5	0 5–3 8	1 3–12 7	5 6–21.1
(20) Mean	55	6.3	2 1	6.0	14 4
Myocardial Infarction					
(23) Range	42–81	0.6–9 6	0–2 5	1 9–16 2	2 7–23 8
(23) Mean	57	3 7	0 7	6 4	10 8
Bantus					
(21) Range	20–45	2 0–11 3	0–6 4	0 8–6 4	5 0–21 0
(21) Mean	31	5 5	2.5	3 5	11 5

Note Figures in parenthesis refer to the number of subjects studied (from Bersohn and Oelofse[26, 27])

group of healthy men and to a group of men with recent myocardial infarction They found that the sum total of estrone, estradiol and estriol recovered in the urine, as a percentage of the dose, was the same in the two groups however, the men with myocardial infarction excreted relatively more of the urinary estrogen as estriol than the control group This is in agreement with the findings of Bersohn and Oelofse[26] for the excretion of endogenous estrogens. Further work using technics which measure all the metabolites of estradiol is obviously necessary before the significance of these results can be ascertained.

Liver Disease

The liver is the main organ in the body responsible for the metabolism of the estrogenic hormones Certain clinical conditions, such as gynecomastia, testicular atrophy and menstrual disorders commonly associated with liver disease, have therefore been ascribed to failure of the liver to inactivate the estrogens normally produced in the body.

Cameron[23] measured the output of urinary estrogens in 12 patients with chronic liver disease. All had diffuse liver fibrosis and evidence of functional damage but none was moribund. Total estrogen excretion was abnormal in only 2 cases These were men who were excreting 42 and 35 micrograms/day; in one, the output of all 3 estrogens was increased, in the other, only estriol was increased. However, 4 patients were excreting higher proportions of estriol to total estrogens than normal. No unconjugated estrogen was detected in the urine of any case. Bloomberg et al [24] obtained similar results in a comparison of the estrogen output of a group of 5 men

with cirrhosis of the liver and a control group of 10 healthy men. Individual values were not reported, but as a group, the patients with cirrhosis excreted larger amounts of total estrogens than the control group, and again, this increase was confined mainly to the estriol fraction. The writer (unpublished observations) has also found that the output of urinary estrogens may sometimes be increased in liver disease, and that this increase usually includes the estriol fraction. These findings are not in accord with the belief that estrogen metabolism is impaired in these cases. In fact, the moderately diseased liver seems to be even more effective in metabolizing estrogens than the normal, at least in so far as the pathway to estriol is concerned.

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THE RELATIONSHIP BETWEEN URINARY ESTROGEN EXCRETION AND CLINICAL SIGNS OF ESTROGENIC ACTIVITY

The His[illegible] of the Endometrium

From their study o[illegible] and 16 women h[illegible] show a close co[illegible] in the urine and [illegible] divided their subjects into two main groups according to whether [illegible] ere excreting amounts of estrogens which remained more or less constant from day to day (type I)

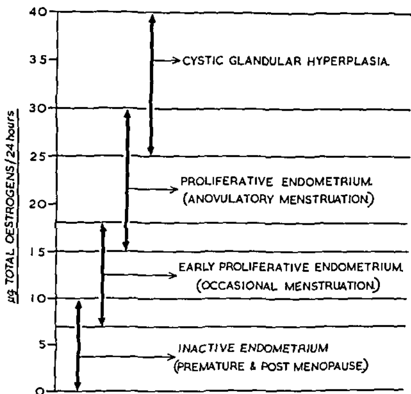


FIG 5—Correlation between urinary estrogen excretion and endometrial pattern (constant estrogen excretion) [13]

or which showed pronounced periodic fluctuations (type II). Each group was further subdivided according to the histologic appearance of the endometrium The estrogens, expressed as micrograms total estrogens excreted/24 hours, found in each of the subdivisions, are summarized in figures 5 and 6 (Figure 6 incorporates the applicable features of figure 5).

A certain amount of overlap was observed between the estrogen values found in each of the subdivisions This is not surprising when account is taken of such variable factors as endometrial response and duration of endometrial stimulation.

Vaginal Cytology

Young, Bulbrook and Greenwood[29] compared the cellular patterns of the vaginal fluid with the output of the 3 estrogens in the urine in 53 premenopausal and postmenopausal women. Seventy-five observations were made, most of them on random samples. They used 7 methods of grading the estrogenic response of the vaginal cells and obtained a close correlation between all of these and the output of estriol in the urine. However, no

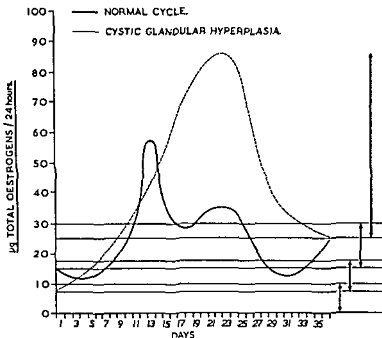


Fig 6—Correlation between urinary estrogen excretion and endometrial pattern Values for the ovulatory menstrual cycle and cystic glandular hyperplasia (fluctuating estrogen levels) superimposed on the data given in fig 5 [13]

such universal correlation was obtained for estrone and estradiol excretion

Puttarajurs and Taylor[30] collected serial vaginal smears and urine specimens throughout the menstrual cycles of 4 women and compared the degree of cornification of the vaginal epithelium with estrogen excretion They showed that during the follicular phases of the cycles studied, some correlation between total urinary estrogens and the degree of vaginal cornification could usually be shown This correlation was most significant when the estrogen output was compared with the smear taken two days later

The above relationships between urinary estrogen excretion and clinical signs of estrogenic activity have been established for women only, in whom the ovaries are the main source of estrogen Similar studies have not yet been attempted in patients with adrenocortical hyperfunction or in men. The apparent anomaly that normal men may excrete as much estrogen as women during the first week of the menstrual cycle or during anovulatory cycles and yet do not experience enlargement of the breasts, indicates that androgens have an important effect on the response of target organs to estrogenic stimulation.

Conclusions

This article is not a complete review of the subject. For example all the recent work on the estimation or urinary estrogens in normal and abnormal pregnancy and in the new born has been omitted (see, for example refs. 31 and 32). The main aim has been to show that determinations of the amounts of estrone, estradiol-17β and estriol excreted in the urine can, in certain conditions, provide the clinician with valuable information. It should be emphasized that the results of single assays performed on random samples of urine may often be misleading The assay methods used to obtain most of the data reported here are too elaborate and costly for routine clinical use, they can only be undertaken in a well equipped laboratory devoted to the purpose However, now that the value of these assays is established, there is a need for simplification of the technics so that they can become more universally available.

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11

Urinary Pregnanetriol: A Practical Determination in Clinical Medicine

By ALFRED M BONGIOVANNI, M.D.

THE ADRENOGENITAL SYNDROME, due to congenital adrenocortical hyperplasia, is an "inborn error of metabolism" wherein the adrenal cortex is partly or totally disabled in its biosynthesis of hydrocortisone.[1] The oxidation of the steroid nucleus is required, at several positions, for the realization of this goal In the most common form of the disease, the oxidation of the C-21 position is poorly, if at all accomplished, due to a deficiency of "21-hydroxylase " As a result, numerous species of C-21 methylated steroids appear in the urine, among them, pregnane-3α, 17α, 20α triol (hereafter designated pregnanetriol) While present in only small quantities in the urine of normal individuals, it is greatly increased in patients with the adrenogenital syndrome, representing an interruption in the biosynthetic pathway at the level of 17-hydroxyprogesterone, of which pregnanetriol is the completely reduced metabolite. The defect is different in the hypertensive form of the disorder, wherein "11-hydroxylase" instead of "21-hydroxylase" is lacking, in spite of which the excretion of pregnanetriol may be moderately increased

This disorder is characterized clinically by masculinization [2] The female is often born with ambiguous external genitalia and the male exhibits isosexual precocity The urinary 17-ketosteroids are generally elevated, but the degree of rise is sometimes slight, particularly in young infants Under these circumstances, measurement of the pregnanetriol excretion is valuable Furthermore, the elevation of pregnanetriol is a more specific indication of the basic disorder Pregnanetriol was not increased in 6 virilizing tumors of the adrenal cortex which we have studied, but it cannot be said with certainty that it is invariably normal in the presence of such neoplasms. *Although the urinary corticoids should be diminished in the adrenogenital syndrome, often they are not* Since the defect is frequently partial, the block may be overcome as a result of the excessive adrenocorticotropic stimulation, so that normal quantities of corticoids are secreted, but this can only occur at the cost of an increase in urinary pregnanetriol Another form of the disease is accompanied by salt and water loss with shock and early death, unless suitable treatment is instituted early In this type, the pregnanetriol is usually very high.

The estimation of urinary pregnanetriol is, therefore, of diagnostic value.

It also serves as an index of adequate treatment with hydrocortisone or its analogues; urinary excretion should be restored to normal. When treatment is inadequate or in the face of impending relapse, the urinary pregnanetriol tends to rise before the 17-ketosteroids.

Method

The method to be described has been employed for several years and has been found to be reliable. It is based on the enzymatic hydrolysis of urine, extraction, chromatography and the development of chromogens by the addition of concentrated sulfuric acid The color produced is unique among the steroids A critical analysis of this method has been published [4] Less discriminating methods are not permissible when sulfuric acid is employed to induce chromogenicity, since many other compounds produce spurious colors under these circumstances The term "pregnanediol complex," measured by the addition of sulfuric acid to crude residues, is without sanction

Reagents

1 Beta-glucuronidase (Ketodase, Warner-Chilcott, 5,000 Fishman units/milliliter)

2 Acetate buffer, 1 0 M, pH 4 5

3 Dichloromethane (Fisher, reagent grade) purified by redistillation from anhydrous sodium carbonate

4 Concentrated sulfuric acid (Mallinckrodt analytic reagent).

5 Redistilled benzene (Merck reagent)

6 Absolute ethanol (Commercial Solvents)

7 Alumina (catalyst, Harshaw) This is generally employed as supplied, provided the moisture content is 3 65 to 3 85 per cent

8 Spectrophotometer, Beckman, Model DU

Procedure

1 *Urine Collection:* Urine is collected for exactly 24 hours in a vessel containing several milliliters of toluene This should be delivered to the laboratory within 24 hours of completion and should be stored below 10 C. It appears that pregnanetriol may be accurately estimated on specimens so stored for several weeks

2. *Hydrolysis* A 10 milliliter aliquot is incubated with 1 0 milliliter acetate buffer and 5,000 units glucuronidase at 37 C. for 16 to 24 hours.

3 *Extraction:* The urine is extracted 3 times with 10 milliliters dichloromethane and the pooled extract is washed twice with 10 milliliters 0.1 N. sodium hydroxide and twice with 10 milliliters water. The extract is evaporated to dryness with a stream of air at 40 to 50 C

4. *Preparation of Column:* A glass column, 4 to 6 mm. internal diameter with a reservoir capacity of 75 to 150 milliliters is filled with a slurry of alumina and benzene so that a height of 7 cm. alumina is achieved. The bottom and top of the alumina column *is plugged with a small piece of* glass wool

5 *Chromatography* The residue of the urine extract is dissolved with gentle heat in 10 milliliters benzene and poured on the column. This is followed by 20 milliliters benzene which is rinsed through the flask containing the original residue, and 40 milliliters of a 2.0 per cent solution of ethanol in benzene These eluents are discarded. The final eluent consists of 30 milliliters 6 0 per cent solution of ethanol in benzene, this is collected in a clean flask and evaporated to dryness as before In order to remove traces of benzene, 2 0 milliliters absolute ethanol are added and evaporated to dryness Air pressure may be used throughout to hasten the flow a solvent flow of 3 to 4 milliliters/minute is permissible.

6 *Color Development·* To the residue of the final eluent 10 milliliters of concentrated sulfuric acid are added After 30 to 120 minutes at room temperature, the absorbance is determined at 390, 410, 425, 440 and 470 millimicrons Standards of pregnanetriol, if available, are treated with sulfuric acid and measured simultaneously in concentrations of 10 to 40 micrograms/10 milliliters acid

7. *Calculation* The maximum absorption will be observed at 440 mμ if a significant quantity of pregnanetriol is present With many normal urine samples containing *very small quantities this will not be the case A correction factor* is employed

$$D_{corr} = \text{absorbance at } 440 \text{ m}\mu - (410 \text{ m}\mu + 470 \text{ m}\mu)/2$$

The total quantity of pregnanetriol is calculated on the basis of the total urine volume and by comparison with the standards If a pure standard is not available, the following factor may be employed with reduced accuracy

$$E_{1\,cm}^{1\,\text{per cent}} \text{ corrected at } 440 \text{ m}\mu = 458$$

In the presence of large quantities of pregnanetriol, as may be surmised by the amount of dried residue of the final eluate, a smaller aliquot is to be treated with sulfuric acid. Alternately, following the development of intense color with the sulfuric acid, the sample may be further diluted with acid. Urine from normal subjects usually requires less than 10 milliliters concentrated sulfuric acid, but for diagnostic purposes the accurate determination of small quantities is not imperative.

8. *Quantities of Pregnanetriol in Human Urine.* The quantities measured vary with the age of the subject, whether normal or diseased. In the first

few days of life, we have detected no pregnanetriol whatsoever in a large series of normal infants, hence the occurrence of small quantities with typical chromogens at this age is significant. The values, indicated as milligrams pregnanetriol/24 hours, are shown in the table:

Age (yrs)	Normal		Adrenogenital Syndrome	
	range	mean	range	mean
0-6	0-0 2	0 02	0 7-13 4	5 8
7-16	0 3-1 1	0 6	5 5-40 0	16 7
over 16	0 2-3 5	1 53	8 4-60 0	33 0

Alternative Methods

1 *Paper Chromatography* The urinary extract may be resolved by paper chromatography instead of column chromatography, followed by elution from the paper, evaporation to dryness and the addition of concentrated sulfuric acid as above However, it is advisable to remove matter derived from the paper, which unavoidably contaminates the residue, by filtration through alumina A satisfactory system is that of Bush consisting of benzene 500 milliliters, methanol 250 milliliters and water 250 milliliters.[3] The extract of 10 ml urine is applied to a sheet approximately 6 inches wide. By the descending technic, pregnanetriol migrates about 25 0 cm. when the solvent front is 38 cm from the starting line It is necessary to locate the position of pregnanetriol by use of a pure standard on a narrow region of the same sheet, or by staining a narrow strip from the center with the phosphomolybdate reagent

2 *Periodate Oxidation without Chromatography* The urine residue may be directly oxidized with periodate according to the method of Cox.[4] The amount of acetaldehyde produced is a measure of the quantity of pregnanetriol and other C-21 steroids which have the same significance. This method eliminates the necessity for chromatography but requires especially rigid technic, and has proven difficult for the average technician However, it is an elegant tool and may lend itself better to some laboratories The results, employing pregnanetriol as a standard, are 15 to 50 per cent higher than those recorded above due to the presence of other compounds with a side chain identical to pregnanetriol Nonetheless, there is a clear division between normal and abnormal levels

Caution The 20β isomer of pregnanetriol is more easily obtained than the 20α The sulfuric acid chromogens and acetaldehydogenic properties of the two are identical, but the chromatographic behaviors are quite different Hence the 20β isomer is *not* suitable for the determination of recoveries when chromatography is employed. However, they may be used

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Urinary Aldosterone

By ELEANOR H. VENNING, M Sc., Ph.D., F.R S C

THE DEVELOPMENT OF ASSAY METHODS for aldosterone, the sodium-retaining hormone isolated from the adrenal cortex by Simpson and Tait in 1952, has followed the pattern observed with other corticosteroids.

The original methods were biologic and were designed to measure the specific effect of aldosterone or of other mineralocorticoids on sodium and potassium excretion in adrenalectomized laboratory animals Early methods include those of Dorfman et al (1947), Deming and Luetscher (1950), Spencer (1950), Simpson and Tait (1952), Kagawa et al (1952) and Singer and Venning (1953) These methods were used not only to measure the effect of adrenal hormones on electrolyte metabolism but were also applied to urinary extracts to determine their sodium-retaining effect.

At first, crude neutral urinary extracts were used which were obtained by extraction of urine at neutral pH with chloroform and these contained only the free hormone Little activity could be detected in this fraction from normal urine although a sodium-retaining effect could be demonstrated in extracts obtained from the urine of patients with nephrosis and liver cirrhosis associated with edema In 1955 Luetscher showed that mild acid hydrolysis released additional amounts of aldosterone Aldosterone is apparently excreted in urine in the form of an unidentified conjugate which is hydrolyzed at pH 1, at room temperature over a period of 24 to 48 hours Recently Ulrich and Lieberman (1957) have reported the isolation of a reduced metabolite of aldosterone conjugated with glucuronic acid This metabolite is inactive

The assay of crude extracts by bioassay is open to criticism as other adrenal corticosteroids as well as toxic material are present which may affect sodium metabolism in the adrenalectomized rat. Simpson and Tait (1955) obtained an effective separation of aldosterone from cortisone in adrenal extracts by the use of two paper chromatographic systems, the toluene propylene-glycol system of Zaffaroni and the C system of Bush. At the present time, urinary extracts are usually subjected to a preliminary purification using column or paper chromatographic procedures before bioassay

Although the bioassay has serious limitations because of its low order of accuracy, it still has many uses and is of particular value in the search for new biologically active steroids.

interchangeably for standards when sulfuric acid is added directly to the steroid.

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group. The recovery of aldosterone added to urine and carried through the whole procedure averaged 75 per cent

2 Nowaczynski et al (1956) showed that the fraction of aldosterone obtained after these two chromatographic separations contained small amounts of at least four other compounds and proposed the introduction of a third system, that of Eberlein and Bongiovanni (E_2B). In the following year, these authors[6] proposed a preliminary purification of urinary extracts on silica gel columns The separation of the pure aldosterone fraction was accomplished by the use of 3 paper chromatographic systems, propyleneglycol/toluene, iso-octane/butanol/water and benzene/55 per cent aqueous methanol Aldosterone was measured by the reaction with blue tetrazolium and an ultraviolet absorption curve. When the hormone was added to urine, 83 per cent could be recovered by this procedure.

Other investigators have also suggested that more than two chromatograms are necessary in order to obtain a pure aldosterone fraction, Gornall and Quilliam, 1957 and Hernando and co-workers, 1957.

3 Our investigations on chemical and bioassay procedures for the assay of aldosterone indicate that extensive purification of the aldosterone fraction must be carried out in order to obtain agreement between values measured by ultraviolet absorption, reduction with blue tetrazolium and bioassay Dyrenfurth et al[7] have reported our findings and suggested a sequence of four chromatographic separations on paper. The systems used were those of Zaffaroni, Bush C, E_2B and Bush B_5. When aldosterone was added to urine, a loss of 15 per cent occurred in the hydrolysis and extraction procedure and a further loss of 25 per cent was observed during chromatography in the four systems The total recovery averaged 60 per cent

4 Recently Ayers et al[8] have described an isotope dilution method for the assay of aldosterone, cortisol and corticosterone after continuous extractions of urine at pH 1, by chloroform for 24 hours at room temperature Paper chromatography of the steroids or their acetyl derivatives follows the extensive preliminary purification by column chromatography The final spot on the paper chromatogram is measured quantitatively by a fluorimeter after development with a solution of sodium hydroxide Recovery of steroids throughout the whole procedure is of the order of 70 per cent.

Excretion of Aldosterone in Normal Individuals

The amount of aldosterone that can be extracted from a 24 hour collection of urine varies to some extent on the methods of hydrolysis and extent of purification by chromatography Continuous extraction of urine at pH 1 [illegible]

Bioassay Methods

The following bioassay procedures have been used extensively for measuring urinary aldosterone

1 Simpson and Tait[1] injected simultaneously small amounts of Na^{24} and K^{42} into young male adrenalectomized rats and measured the effect of aldosterone upon the ratio of Na^{24} to K^{42} Aldosterone was 120 times as active as desoxycorticosterone in causing a depression of this ratio.

2 Venning et al [2] administered 3 5 mg. of NaCl to adrenalectomized male rats weighing 165 to 180 Gm. and measured the effect of aldosterone on sodium excretion Urinary sodium was determined by flame photometry. A linear relationship was obtained between the log dose of the standard material and the response of the test animals, expressed as a percentage of the controls. Aldosterone was 25 times as active as DCA in this assay.

3. Johnson[3] used 3 groups of adrenalectomized female rats (150 to 160 Gm.) Control solvent, standard and material to be tested were injected into each group of rats on three successive days in order to eliminate variations in animal response. Urinary sodium and potassium were measured by flame photometry and the K/Na ratio was used as an index of aldosterone activity Aldosterone was 35 times as active as DCA in this assay

4 Liddle et al [4] developed a bioassay for aldosterone based on the use of adrenalectomized dogs fed a constant high sodium diet and measured urinary sodium and potassium Aldosterone was 30 times as active as DCA in this assay

Chemical Procedures

The inherent variability of the bioassay methods has encouraged investigators to search for satisfactory chemical or physicochemical methods for measuring aldosterone These are all based on the original observations of Simpson and Tait with regard to the separation of aldosterone by chromatographic procedures As the final determination of aldosterone depends on group reactions which are common to many corticosteroids, the necessity of obtaining a pure fraction is obvious Reactions that have been used to evaluate aldosterone are sodium fluorescence, ultraviolet absorption of the Δ^4 keto group in ring A, the formazan color measuring the α ketol group and the formation of dinitrophenylhydrazones by the keto groups

1 Neher and Wettstein proposed a physicochemical procedure in 1955 which was later modified in 1956.[5] Two systems of paper chromatography were used, the chloroform-formamide system of Zaffaroni and that of Bush C Two combined color reactions were used to measure the aldosterone spot, one depending on the reducing properties of the α-ketol side chain with blue tetrazolium and the second the soda fluorescent property of the Δ^4-3 ketone

dosterone hold out hope for further clarification regarding the regulation of aldosterone secretion in man

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TABLE 1—*Excretion of Aldosterone in Healthy Individuals on Normal Salt Intake*

Authors	Procedure	µg Aldosterone per 24 hours
Luetscher et al	bioassay[2]	1-7
Venning et al [2]	bioassay	1-9
Neher and Wettstein[5]	physicochemical	1-13
Genest et al [6]	physicochemical	2-10
Venning et al [7]	physicochemical	2-12
Ayers et al [8]	isotope dilution	5-23

metabolite of aldosterone is, however, present as a glucuronide and is isolated on paper by different methods Jones et al. showed that when 16H[3] aldosterone is injected into normal women, 0 24 per cent could be extracted as aldosterone at neutral pH, 5 1 per cent at pH 1, and 39 per cent of the radioactivity was released by β-glucuronidase hydrolysis. The latter was presumably the reduced metabolite.

The values reported for the amount of aldosterone (extractable at pH 1) excreted per 24 hours by normal men and women has gradually increased with improvement in methods of extraction and assay The most recent values reported are listed in table 1.

The range of aldosterone excretion in healthy individuals reported by various investigators agree fairly well with the exception of those determined by the isotope dilution technique, which are much higher

There are many factors which influence aldosterone secretion in the normal person Variations in sodium and potassium intake as well as alterations in body fluid volumes will affect urinary aldosterone excretion. Emotional stress, such as acute anxiety, will cause a significant rise in aldosterone excretion in some healthy individuals.

In adrenal hyperfunction associated with Cushing's disease, aldosterone excretion is usually within the normal range, while in primary aldosteronism values in the range of 25 to 35 µg. per day have been reported. In clinical conditions associated with accumulation of edema, such as congestive heart failure, nephrosis and idiopathic edema, as well as accumulation of ascites in patients with cirrhosis of the liver, increased excretion of urinary aldosterone have been observed In normal pregnancy, there is a significant rise in urinary aldosterone in the last trimester

At the present time, there is no simple method for assaying urinary aldosterone accurately All procedures are time-consuming and require careful separation of the steroid. The amount of aldosterone isolated represents only a small fraction of that secreted by the gland and the metabolism of aldosterone still requires further investigation. The technics that have been developed recently for measuring secretion rates using tritiated al-

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